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Title Supplement .... Phenanthrene

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A supplement to
The Chemistry of Natural Products Related to Phenanthrene

by L. F. Fieser

◆

A reprint of the Appendix of recent literature (to the publication date, January 1, 1937), and revised indexes with page references to the First Edition

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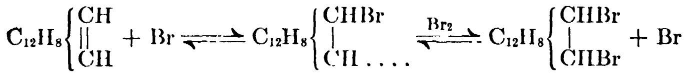
APPENDIX

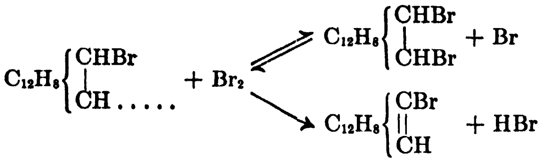
Chapter I

Reaction of Phenanthrene with Bromine (pp. 6-7). From a study of the kinetics of the formation of phenanthrene dibromide, Price, *J. Am. Chem. Soc.*, **58,** 1834 (1936), concluded that the reaction proceeds by a chain mechanism (even in the dark), the chain being propagated by bromine atoms and free radicals:



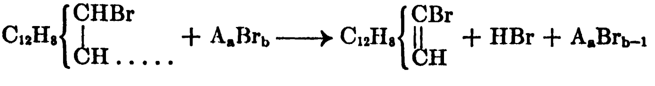
$$C_{12}H_8\left\{\begin{matrix}CH\\ \|\\ CH\end{matrix}\right. + Br \rightleftharpoons C_{12}H_8\left\{\begin{matrix}CHBr\\ |\\ CH\ldots\end{matrix}\right. \overset{Br_2}{\rightleftharpoons} C_{12}H_8\left\{\begin{matrix}CHBr\\ |\\ CHBr\end{matrix}\right. + Br$$

This conclusion was suggested by the observation that the reaction is inhibited by substances such as diphenylamine and tetrabromohydroquinone which can donate atoms of hydrogen to combine with bromine atoms and break the chain, while the inhibitors thereby revert to stable compounds. It is estimated that at 25° the chain consists of about 2,000 molecules, but that the chain length decreases with increasing temperature, accounting for the absence of a temperature coefficient in the measured reaction. Price, *ibid.*, **58,** 2101 (1936), also made the interesting observation that iodine, a typical catalyst for the halogenation of the benzene ring, inhibits the formation of phenanthrene dibromide, probably by interacting with chain-propagating bromide atoms. Furthermore, although iodine catalyzes the formation of hydrogen bromide in a solution containing phenanthrene, bromine, and the dibromide, it appears that the hydrogen bromide does not arise directly from the decomposition of the dibromide, as pictured in the classical addition-elimination theory. On adding iodine to a solution of phenanthrene dibromide in carbon tetrachloride (25°), no hydrogen bromide (or bromine) is produced until a trace of bromine is added, and even then the rate of HBr-formation is no greater than in a solution containing initially equivalent concentrations of phenanthrene and bromine. The addition-elimination theory seems definitely excluded by these observations, and it appears that the addition compound is formed, not as a necessary precursor of 9-bromophenanthrene, but from a radical, or other intermediate, common to both addition and substitution, the course of the reaction depending on the presence or absence of catalysts.



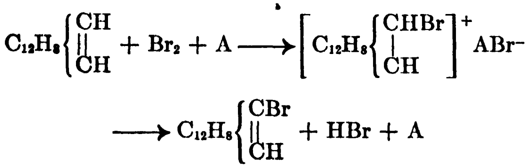
$$C_{12}H_8\left\{\begin{matrix}CHBr\\ |\\ CH\cdots\cdots\end{matrix}\right. + Br_2 \begin{matrix}\nearrow C_{12}H_8\left\{\begin{matrix}CHBr\\ |\\ CHBr\end{matrix}\right. + Br\\ \searrow C_{12}H_8\left\{\begin{matrix}CBr\\ \|\\ CH\end{matrix}\right. + HBr\end{matrix}$$

If a radical is involved in the first phase of the reactions, a catalyst A may function in combination with bromine as a hydrogen acceptor and so influence the rate of substitution.



$$C_{12}H_8\left\{\begin{matrix}CHBr\\ |\\ CH\cdots\cdots\end{matrix}\right. + A_aBr_b \longrightarrow C_{12}H_8\left\{\begin{matrix}CBr\\ \|\\ CH\end{matrix}\right. + HBr + A_aBr_{b-1}$$

As Price notes, it is equally possible that the essential intermediate is a coördinative complex of the type suggested by Pfeiffer and Wizinger, *Ann.*, **461**, 132 (1928).



$$C_{12}H_8\left\{\begin{matrix}CH\\ \|\\ CH\end{matrix}\right. + Br_2 + A \longrightarrow \left[C_{12}H_8\left\{\begin{matrix}CHBr\\ |\\ CH\end{matrix}\right.\right]^+ ABr^-$$
$$\longrightarrow C_{12}H_8\left\{\begin{matrix}CBr\\ \|\\ CH\end{matrix}\right. + HBr + A$$

The effect of substituents on the phenanthrene-bromine equilibrium was investigated by Fieser and Price, *ibid.*, **58,** 1838 (1936), who found that carboxylic ester groups and halogen atoms in the 2- and 3-positions decrease the free energy of the 9,10-addition of bromine ($-\Delta F_{25}° = 3220$ cal., for phenanthrene), while the *ter.*-butyl group has the opposite effect. The results parallel those obtained in the study of the free energy of oxidation of 9,10-phenanthrenehydroquinones by oxidation-reduction potentials (Ref. 54, p. 14), and there is a correlation between the observed effects of the groups concerned and their influence in retarding or facilitating substitutions in the benzene ring [L. F. Fieser and M. Fieser, *ibid.*, **57,** 491 (1935)].

Friedel and Crafts Reaction (pp. 9-10). The condensation with propionyl chloride in nitrobenzene solution proceeds as in the other cases. Bachmann and Struve, *J. Am. Chem. Soc.*, **58,** 1659 (1936).

Phenanthraldehydes (pp. 10-11). Details of the preparation of 1-phenanthraldehyde[43] by the Sonn and Müller reaction are given by Bachmann and Boatner, *J. Am. Chem. Soc.*, **58,** 2097 (1936). Hinkel, Ayling and Beynon, *J. Chem. Soc.*, 339 (1936), obtained the 9-aldehyde in 44% yield by the condensation of the hydrocarbon with hydrogen cyanide in chlorobenzene solution by means of aluminum chloride. The use of chloromethyleneformamidine in similar syntheses in place of hydrogen cyanide also was investigated.

Considerable attention has been given to the development of general methods for the synthesis of aromatic aldehydes without specific reference to phenanthrene chemistry. F. E. King, L'Ecuyer and Openshaw, *ibid.*, **352** (1936) studied various applications of the methods of Sonn and E. Müller [*Ber.*, **52,** 1927 (1919); **58,** 1096 (1925)] and of Stephen [*J. Chem. Soc.*, **127,** 1874 (1925)]. The latter synthesis consists in the reduction of a nitrile (as the imido chloride) with anhydrous stannous chloride in ether saturated with hydrogen chloride, and hydrolysis of the resulting aldimine complex: $RCN \longrightarrow RC(Cl)=NH \longrightarrow (RCH=NH,HCl)_2SnCl_4 \longrightarrow RCHO$. Wittig and Kethur, *Ber.*, **69,** 2078 (1936), found that certain reductions with anhydrous stannous chloride proceed well in dioxane solution. Maxim and Mavrodineanu, *Bull. soc. chim.*, [5], **3,** 1084 (1936) studied the Bouveault synthesis [Bouveault, *Compt. rend.*, **137,** 987 (1903); Houben and Doescher, *Ber.*, **43,** 3435 (1910)]. In the typical case a Grignard reagent is condensed with N-formanilide and the aldehyde is obtained by hydrolysis of the product: $ArMgBr + OCH \cdot N(CH_3)C_6H_5 \longrightarrow ArCH(OMgBr)N(CH_3)C_6H_5 \longrightarrow ArCHO + BrMgN(CH_3)C_6H_5$. An entirely new method, reported by McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936), consists in the alkaline hydrolysis of a benzenesulfonacylhydrazide, the steps in the preparation and decomposition of the intermediate being as follows:

$$ArCO_2C_2H_5 \xrightarrow{H_2NNH_2} ArCONHNH_2 \xrightarrow{C_6H_5SO_2Cl}$$

$$ArCONHNHSO_2C_6H_5 \xrightarrow{KOH} ArCHO + N_2 + C_6H_5SO_2K.$$

The application is limited to the aromatic series. Another new method of transforming carboxylic acids into aldehydes, particularly useful in the case of aldehydes of a sensitive nature, is that of C. Grundmann, *Ann.*, **524,** 31 (1936). The method involves the following steps:

$$RCOCl \xrightarrow{CH_2N_2} RCOCHN_2 \xrightarrow{CH_3CO_2H} RCOCH_2OCOCH_3 \xrightarrow{H_2}$$

$$RCH(OH)CH_2OH \xrightarrow{Pb(OCOCH_3)_4} RCHO + HCHO$$

9-Phenanthrol (p. 11). Fieser, Jacobsen and Price, *J. Am. Chem. Soc.*, **58,** 2163 (1936), found that on treatment with bromine in methanol solution, phenanthrene is converted into an unstable complex consisting apparently of one molecule each of phenanthrene methoxybromide and phenanthrene dibromide. The complex yields 9-methoxyphenanthrene and phenanthrene when warmed with alcoholic potassium hydroxide-acetate, and 9-phenanthrol is easily obtained from the mixture in 28-30% yield, based on the phenanthrene consumed. The synthetic preparation of 9-phenanthrol is discussed on page 356.

Phenanthrylamines (addition to p. 12). A very satisfactory method of preparing the 2- and 3-amino derivatives of phenanthrene was discovered by Bachmann and Boatner, *J. Am. Chem. Soc.*, 58, 857, 2097 (1936), and employed in independent work by Mosettig and J. W. Krueger, *ibid.*, 58, 1311 (1936) and by Fieser and Price, *ibid.*, 58, 1838 (1936). The oximes of 2- and 3-acetylphenanthrene, prepared advantageously in pyridine solution, are submitted to the Beckmann rearrangement and the resulting acetylaminophenanthrenes are hydrolyzed to the amines. Bachmann and Boatner found that the rearrangements with phosphorus pentachloride proceed smoothly in benzene solution and that only traces of the alternate products, $C_{14}H_9CONHCH_3$, are formed. They prepared the new 1-phenanthrylamine by this method, the 1-acetylphenanthrene required being synthesized for the purpose from both 1-phenanthroic acid and 1-phenanthraldehyde. Details of the preparation of 1-phenanthroic acid from 1-benzoylphenanthrene are included in the paper, the process consisting in the Beckmann rearrangement of the oxime and the acid hydrolysis of the anilide at 200° (compare Ref. 33).

9-Phenanthrylamine was obtained by Bachmann and Boatner from the 9-acetyl derivative which, in turn, was prepared by the action of methylmagnesium iodide on 9-cyanophenanthrene. A shorter process consists in heating 9-phenanthrol with ammonium sulfite and ammonia, following the general procedure of Bucherer [Fieser, Jacobsen and Price, *ibid.*, 58, 2163 (1936); compare Russ. Pat. 40,988 (1935)].

Phenanthryl Halides (addition to p. 12). Since 2- and 3-phenanthrylamine are now readily available through the acetylphenanthrenes, they form convenient starting materials for the preparation of the corresponding halides [Bachman and Boatner, *J. Am. Chem. Soc.*, 58, 857, 2194 (1936); see also Fieser and Price, *ibid.*, 58, 1838 (1936)]. 1-Phenanthryl halides can be obtained similarly from the less accessible amine. Bachmann and Boatner (second paper) found it advantageous to effect the diazotizations by the procedure which de Milt and Van Zandt, *ibid.*, 58, 2044 (1936), developed for use with weakly basic or insoluble amines. A solution of the amine in pyridine is added to a stirred solution of nitrosylsulfuric acid in 2:1 sulfuric acid at 0°. For the introduction of chlorine or bromine atoms, Schwechten's modification of the Sandmeyer reaction proved very satisfactory [Schwechten, *Ber.*, 65, 1605 (1932)]. This involves the precipitation and thermal decomposition of a complex, formed by interaction of the diazonium compound with mercuric halide and potassium halide.

9,10-Dihydrophenanthrene (p. 13). Further details of the preparation[34] of the hydrocarbon are reported by Burger and Mosettig, *J. Am. Chem. Soc.*, **58**, 1857 (1936).

Steric Hindrance (p. 13). Whereas the alkaline hydrolysis of 1′,3′-diketo-1,2-cyclopentenophenanthrene proceeds in both possible directions, the cleavage of 1′,3′-diketo-3,4-cyclopentenophenanthrene occurs exclusively adjacent to the less hindered carbonyl group at C_3, and results in the formation of pure 4-acetyl-3-phenanthroic acid. On decarboxylation this yields the new 4-acetylphenanthrene, L. F. Fieser, M. Fieser, and Hershberg, *J. Am. Chem. Soc.*, **58**, 2322 (1936).

Oxidation of Phenanthrenequinones (p. 15). In the oxidation of retenequinone (1-methyl-7-isopropylphenanthrenequinone) with hydrogen peroxide, a lactone similar to that described by Fieser[27] is formed as a by-product along with the corresponding diphenic acid. Adelson, Hasselstrom and Bogert, *J. Am. Chem. Soc.*, **58**, 871 (1936).

Structure of Pyrene (p 17). A theoretical discussion of the problem, based upon spectroscopic evidence, is given by Clar, *Ber.*, **69**, 1671 (1936).

Substitution Reactions of Chrysene (p. 18). Funke and co-workers (Eugen Müller, Vadasz, and Ristic), *J. prakt. Chem.*, **144**, 242, 265 (1936); **145**, 309 (1936); **146**, 151 (1936), found that chrysene can be converted in good yield into a monobenzoyl derivative, while in the Friedel and Crafts reaction with acetyl chloride a similarly substituted acetyl compound is the chief product but is accompanied by an isomer. Dibenzoyl derivatives were obtained by direct substitution and through a dibromochrysene, and various transformations are reported. Structures are assigned to the new compounds, but the evidence is still incomplete.

Pschorr Synthesis (pp. 28-31). Sharp, *J. Chem. Soc.*, 1234 (1936), employed the Pschorr synthesis for the preparation of 9-acetylamino-2,3,4,6-tetramethoxyphenanthrene, a compound of interest in connection with the chemistry of colchicine (p. 38). Ruggli and Staub, *Helv. Chim. Acta*, **19**, 1288 (1936), have shown that the function of the carboxyl group in the general synthesis is in part to control the condensation in such a way that the stilbene derivative is in the steric condition suitable for subsequent cyclization.

Sinomenine (p. 37). Further studies are reported by Goto and co-workers (Shishido, Ogawa, Saito), *Bull Chem. Soc. Japan*, **10**, **252**, **481**, 597 (1935).

References to the Work on Drug Addiction (pp. 45-48). Chemical investigations of alkaloids of the morphine group are reported by Small and coworkers (Lutz, Mosettig, F. L. Cohen, Faris, Yuen, Fitch, W. E.

Smith, Morris and Eilers) under the following headings: **desoxycodeine studies,** *J. Am. Chem. Soc.*, **53,** 2214, 2227 (1931); **54,** 793, 802 (1932); **56,** 1738 (1934); **reduction studies,** *ibid.*, **54,** 4715 (1932); **56,** 1741, 1928, 2466 (1934); **57,** 361, 364, 2651 (1935); **Grignard reaction,** *ibid.*, **58,** 192, 1457 (1936); **miscellaneous,** *ibid.*, **55,** 2874, 3863 (1933); **56,** 1930 (1934); *J. Org. Chem.*, **1,** 194 (1936). The synthetic work of Mosettig and coworkers (van de Kamp, Burger, J. W. Krueger, R. A. Robinson) is reported as follows: **phenanthrene derivatives,** *J. Am. Chem. Soc.*, **52,** 3704 (1930); **54,** 3328 (1932); **55,** 2981, 2995, 3442, 3448 (1933); **56,** 1745 (1934); **57,** 1107, 2189 (1935); **58,** 1311, 1568, 1570, 1857 (1936); **dibenzofuran derivatives,** *ibid.*, **57,** 902, 2186 (1935); **58,** 688 (1936).

Pharmacological studies of the **synthetic compounds** by Eddy and by R. G. Smith are reported in the series: *J. Pharmacol.*, **48,** 183 (1933); **51,** 75, **52,** 275 (1934); **54,** 87 (1935); **55,** 354, 419 (1935); **58,** 159 (1936). Pharmacological studies of the alkaloids by Eddy, Simon, Aherns, Reid, Howes, H. Krueger, Gay, Lampe, C. I. Wright, Barbour and Foster are reported thus: **general physiological actions,** *ibid.*, **45,** 339, 361 (1932); **49,** 319 (1933); **51,** 35 (1934); *Am. J. Psyc.*, **47,** 597, 614 (1935); *J. Pharmacol.*, **52,** 468 (1934); **53,** 430 (1935); **55,** 127, 257 (1935); **56,** 421 (1936); **action on intestinal movement,** *ibid.*, **50,** 254, **51,** 85, 440 (1934); **55,** 288 (1935); **56,** 327 (1936); **respiratory effects,** *ibid.*, **51,** 327, 343 (1934); **53,** 34, **54,** 25 (1935); **56,** 39 (1936); **effect on blood pressure,** *ibid.*, **51,** 153, 170 (1934).

Chapter II

Chemistry of Retene (addition to p. 58). Studies of various derivatives and oxidation products of retene are reported by Bogert and his co-workers Hasselstrom and Adelson, *J. Am. Chem. Soc.*, **53,** 3462 (1931); **56,** 983 (1934); **57,** 1579 (1935); **58,** 653, 871, 2236 (1936). Nyman, *Ann. Acad. Sci. Fennicae*, **A41,** No. 5, 80 (1934), prepared dihydroretene in good yield by reduction with sodium and amyl alcohol. The acetylation of the dihydro derivative was investigated and a number of new compounds described.

Primary Resin Acids (p. 68). As the result of further investigations, the previous views regarding the nature of the primary constituents of oleoresins and of their relationship to abietic acid have undergone revision. While it appeared from the work of Kraft[57] and of Hasselstrom and Bogert[58] that the crystalline acid mixtures obtained from fresh oleoresins contain only *d*-pimaric acid and levopimaric acid in varying proportions, Kraft, *Ann.*, **524, 1** (1936), in a later investigation discovered a third acid called **pro-abietic acid** ($C_{20}H_{30}O_2$), m.p. 159-160°,$[\alpha]_D$ +11.5°, absorption maximum 243 mμ. This substance was isolated from the crystalline acids of *P. palustris* and from French galipot (*P. maritima*). With aqueous ammonia the acid mixture gives a crystalline precipitate of ammonium salts, from which pure *d*-pimaric acid and levopimaric acid can be obtained by fractional crystallization of the sodium salts. The new acid forms a very soluble ammonium salt and is found in the material precipitated from the ammoniacal mother liquor by neutralization with carbon dioxide. Pro-abietic acid is isomerized to abietic acid by boiling glacial acetic acid or by the action of alcoholic hydrochloric acid at room temperature. In the latter case the progress of the isomerization can be followed by the change in the optical rotation of the solution. From the character of the curve, in comparison with that for levopimaric acid, Kraft suggested that pro-abietic acid may be an intermediate product in the rearrangement of levopimaric acid to abietic acid. Although the acid is present in crystalline products obtained from fresh oleoresins under very mild conditions and without the use of acids, it may not be a true primary acid. The work of Wienhaus, Ritter and Sandermann, *Ber.*, **69, 2198** (1936), indicates that isomerizations may occur even in neutral solvents. They obtained abietic acid from *P. silvestris* without using acids but by repeated crystallization from methanol. *d*-Pimaric acid and levopimaric acid are possibly the only diterpene acids initially present in oleoresins. Probably all of the so-called primary acids described in the literature, other than the two substances mentioned above and Kraft's pro-abietic acid, are mixed crystals containing varying amounts of these three acids and possibly abietic acid.

Further information concerning the structures of the acids and the relationship between them was obtained by Bacon and Ruzicka, *Chemistry and Industry*, **55, 546** (1936), who made the significant observation that levopimaric acid reacts with maleic anhydride at room temperature and yields a product, m.p. 227°, identical with that resulting from the addition of the anhydride to abietic acid. As the latter reaction occurs only at a temperature above 100°, it is inferred that the isomerization of levopimaric acid to abietic acid is reversible and that the conversion of the more stable isomer into the addition product proceeds through an isomerization at the elevated temperature to levopimaric acid. The observation was confirmed in independent work by Wienhaus and Sandermann, *Ber.*, **69, 2202** (1936), who found also that levopimaric acid, but not abietic acid, reacts at room temperature with benzoquinone and with α-naphthoquinone to give beautifully crystalline, yellow products.

Since the other constituents of oleoresins do not form addition products under the same conditions, the reaction offers promise of providing a method for the quantitative determination of levopimaric acid in the resins.

Kraft's early suggestion[57] that levopimaric acid is a bicyclic compound containing three conjugated double bonds (p. 68) has not been substantiated. Bacon and Ruzicka found that, although the acid yields only a dihydro derivative when hydrogenated in neutral solvents in the presence of Adams' catalyst, dihydrolevopimaric acid rapidly absorbs one mole of hydrogen in acetic acid solution, using the same catalyst. From the mixture of stereoisomers produced there was isolated a tetrahydro derivative, m.p. 195-197°, which gives no coloration with tetranitromethane, indicating the absence of a double linkage. The molecular refraction of the methyl ester agrees with that calculated for a tricyclic system and the ester yields retene on dehydrogenation with palladium charcoal. The conclusion that levopimaric acid contains three rings and two double bonds was reached independently by Kraft, in the work cited. Ozonization of levopimaric acid in the cold gave no formaldehyde, contrary to the requirements of the early formulation, and dihydrolevopimaric acid absorbed but a single atom of oxygen on titration with perbenzoic acid. Titrations of levopimaric acid itself also indicated the presence of two double bonds. Kraft originally suggested that the acid contains a triene system because this seemed to account for the displacement of the ultraviolet absorption band in the direction of longer wave lengths, as compared with abietic acid, but he later recognized that the absorption maximum at 272.5 mμ is indicative, rather, of the presence of two conjugated double bonds in the same ring (see p. 374). In analogy with other cases, the absorption maximum of 237.5 mμ found for abietic acid indicates the presence in this acid of two conjugated double bonds distributed between two rings. In view of the evidence that one of the ethylenic linkages extends to the carbon atom (7) carrying the isopropyl group (p. 60), it is probable that the double bonds of abietic acid are located at the 7,8-, and 14,9-positions (for the numbering system, see p. 59). To account for the ready interconversion of abietic acid and levopimaric acid, it is suggested that the latter substance has the Δ7,8;14,13-structure. The double bond of the maleic anhydride addition product is assumed to occupy the 8,14-position. This is consistent with the observation of Wienhaus and Sandermann (*loc. cit.*) that the addition product, as the methyl ester $C_{25}H_{34}O_5$, yields on ozonization a keto ester-acid $C_{25}H_{34}O_8$. This product must arise from the severing of a linkage extending to a bridge head, as at the 8,14-, 5,13-, or 9,14-position. The dihydro derivatives of abietic acid and of levopimaric acid may be structural isomers, or they may differ in the configuration at C_7 or C_{13}. According to this view, pro-abietic acid is not an intermediate isomerization product but has the $\Delta 5,13;14,9$-structure.

Clemmensen Reduction (p. 72). Evidence that the results are often improved by adding toluene to the reaction mixture is presented by Martin,[71] *J. Am. Chem. Soc.*, **58,** 1438 (1936). The modification is particularly useful in the reduction of β-aroylpropionic acids and of certain methoxylated compounds. Fieser and Hershberg, *ibid.*, **58,** 2382 (1936), encountered a remarkable side reaction in the reduction of β-(1,5-dimethoxy-4-naphthoyl)-propionic acid. In the formation of the abnormal product the ketonic group is reduced as usual, but the aromatic ring to which it is attached is hydrogenated in the course of the reaction and a methoxyl group in the para position is eliminated as well.

Friedel and Crafts Reaction with β-Naphthyl Methyl Ether (p. 74). Following the discovery by Haworth that β-naphthyl methyl ether is substituted largely in the 6-position when the Friedel and Crafts reaction with acid chlorides is conducted in nitrobenzene solution (p. 209), Short, Stromberg and Wiles, *J. Chem. Soc.*, 319 (1936), found that this is true also in the reaction with succinic anhydride. They state that in nitrobenzene solution the 6- and 1-substitution products are formed approximately in the ratio 9:1, but no yields are recorded. On using carbon bisulfide as the solvent only the 1-substitution product was isolated (no yield given). Hill, Short and Higginbottom, *ibid.*, 317 (1936), found that when the 1-position is blocked by a methyl group substitution occurs almost entirely in the 6-position. Using nitrobenzene as the solvent they obtained β-(2-methoxy-1-methyl-6-naphthoyl)-propionic acid in 78% yield. The keto acids were employed for the synthesis of 7-methoxy- and 2-methoxy-1-methylphenanthrene.

Synthesis of Retenequinone (p. 75). By a process similar to that of Ruzicka and Waldmann,[75] Keimatsu, Ishiguro and Sumi, *J. Pharm. Soc. Japan*, **56,** 588 (1936), synthesized 9-methoxyretene; retenequinone was obtained on oxidation. As in the work of Ruzicka and Waldmann, the 7-isopropyl-1-naphthyl methyl ether required as starting material was synthesized from isopropylbenzene and succinic anhydride. The synthetic 9-methoxyretene, m.p. 108-108.5°, was identical with the methyl ether of a compound prepared by Fieser and M. N. Young, *J. Am. Chem. Soc.*, **53,** 4120 (1931), by the reduction of retenequinone with zinc dust and acetic acid, and regarded by them as 9-retenol on the basis of certain observations and inferences. The synthesis establishes the fact that it is the oxygen atom closest to the methyl group in retenequinone which is eliminated on reduction.

Perlman-Davidson-Bogert Synthesis (pp. 77-78). Shortly after the preliminary announcement by Bogert[78] in 1933 of the new phenanthrene synthesis, Cook and Hewett (p. 161) reported the independent discovery of the same method. In the hands of Cook and co-workers, and of other investigators, the general scheme of synthesis became an important tool in the solution of various problems, and the method was extended and applied in a number of cases (pp. 22, 164, 167, 210). Cook found that, in the cyclization of an unsaturated hydrocarbon of the type of II, the intramolecular addition of the aromatic nucleus to the double bond usually occurs to some extent in both possible directions, with the result that the normal reaction product is accompanied by an isomeric spiran (pp. 161-162). Eventually a satisfactory method of avoiding spiran formation and improving the yield was developed (Kon, p. 164; Cook, p. 162).

Information concerning the simplest application of the general synthesis has become available only recently. In preparing a quantity of *as*-octahydrophenanthrene (III), van de Kamp and Mosettig, *J. Am. Chem. Soc.*, **58,** 1062 (1936), isolated a small amount of a by-product which they regarded as a stereoisomeric hydrocarbon. From the results of an oxidation experiment, Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936), suggested that the octahydrophenanthrene may be accompanied by a spirocyclic isomer, as in other cases. Finally Bogert and his collaborators reported the results of their study of the reaction [Bogert, *Science,* **84,** 44 (1936); Perlman, Davidson and Bogert, *J. Org. Chem.*, **1,** 288, 300 (1936)]. They were able to separate the by-product in a fairly satisfactory condition and to show that it is a spiran. The hydrocarbon was oxidized to *α,α*-pentamethylenehomophthalic acid, which was identified by comparison with a product obtained by the oxidation of a synthetic spiran of unequivocal structure.

The history of the discovery and exploitation of the important synthetic method is such as to suggest that it be referred to in the future as the Bogert-Cook synthesis.

Darzens Synthesis (p. 80). Darzens and Lévy, *Compt. rend.*, **202,** 73 (1936), found that *α*-chloromethyl derivatives of naphthalene and of *α*- and *β*-methylnaphthalene can be obtained in excellent yield from the hydrocarbon, trioxymethylene, and hydrogen chloride in glacial acetic acid solution. From *α*-chloromethylnaphthalene they obtained 1,9-dimethylphenanthrene by the standard synthesis (c) [*Idem, ibid.*, **202,** 427 (1936)].

Chapter III

1,2-Benzpyrene (p. 83, ff.). The pyrene numbering system used in this book (p. 16) is that originally employed by Cook, Hewett and Hieger,[7] the discoverers of the carcinogenic constituent of coal tar. Some confusion has arisen in the literature because German authors have adhered to the numbering used in early literature and termed the hydrocarbon 3,4-benzpyrene. In the interests of uniformity, the English investigators very recently have reverted to the older system. The present author has agreed to use "3,4-benzpyrene" in future publications, but a change cannot be made in the book until the text is completely revised.

Carcinogenic Activity of Cholanthrene and 1,2-Benzanthracene Derivatives (pp. 88-93). The results of further tests conducted at the Royal Cancer Hospital, London, are reported in review papers by Cook, *Ber.*, **69A, 38** (1936), and by Cook, Haslewood, Hewett, Hieger, Kennaway and Mayneord, *Reports of the Second Congress of Scientific and Social Campaign against Cancer*, **1,** 1 (1936). The results of studies of the carcinogenic action of the hydrocarbons synthesized at Harvard by L. F. Fieser, M. Fieser, Hershberg, Newman and Seligman are reported in detail by Shear,[16,17] *Am. J. Cancer*, **26,** 322 (1936); **28,** 334 (1936). Using the injection technique, and testing the malignant nature of the tissue by transplantation, Shear found that the average time of the appearance of tumors in pure-strain mice following the administration of 5-10 mg. of material affords an approximate relative measure of the potency of the compound. Relative carcinogenic activities determined in this way are as follows: methylcholanthrene, 2.5 mos.; cholanthrene, 3 mos.; 1,2-benzpyrene, 3.5 mos.; 1,2,5,6-dibenzanthracene, 7 mos. Qualitatively, at least, the results are in excellent agreement with those obtained at the Cancer Hospital. A comprehensive review of experiments with 1,2-benzpyrene and 1,2,5,6-dibenzanthracene in a number of other laboratories is given in the paper by Cook, *et al.* (*loc. cit.*)

Since methylcholanthrene and cholanthrene surpass in potency all of the other benzanthracene derivatives previously investigated, it was a matter of considerable interest to attempt to define the features of structure responsible for their striking activity. One aspect of the work in this direction conducted at Harvard was to investigate the effect of further elaborations of the methylcholanthrene molecule. Using the sterol numbering system (p. 111), this potent carcinogenic agent may be called 20-methylcholanthrene, and the introduction of a methyl group at the 16-position in the five-membered ring gives 16,20-dimethylcholanthrene[65] (XIII, p. 107). Shear found that this modification of the molecule results in a distinct decrease in activity, the average time of appearance of tumors being 7.5 mos. 1′,9-Methylene-1,2,5,6-dibenzanthracene[64] (from IX, p. 106) is another compound containing the skeletal structure of methylcholanthrene but having two additional carbon atoms incorporated in an aromatic ring, and it combines as well the features of structure of the carcinogenically active 1,2,5,6-dibenzanthracene. While the hydrocarbon has definite cancer-producing properties, the activity is considerably less than that of the dibenzanthracene (11 mos.). 15,16-Benzdehydrocholanthrene[63] (XVI, p. 107) has the characteristic cholanthrene ring system with a benzene ring fused to the five-membered ring. The substance shows only slight activity.

Although other variations in the same direction would be of interest, it seems evident from the present indications that an increase in the complexity of the structure results in a decrease in carcinogenic activity. The observation that cholanthrene is only slightly less potent than methylcholanthrene suggested that it might be profitable to investigate the further simplification of the molecule. Cholanthrene may be regarded as the 5,10-dimethylene derivative of 1,2-benzanthracene, but, in consideration of its high potency as compared with a number of methyl and dimethyl derivatives of the hydrocarbon, Cook *et al.* were led to conclude that "The essential structural feature is the pentacyclic system present in the molecule." In order to determine with certainty whether the special activity of cholanthrene is associated with the presence of the five-membered ring including carbon atoms 5 and 10, or merely with the presence of alkyl substituents at these positions, Fieser and Newman synthesized 5,10-dimethyl-1,2-benzanthracene (p. 353). The 5- and 10-monomethyl compounds were prepared for comparison. According to the latest (unpublished) observations of Shear, 5,10-dimethyl-1,2-benzanthracene produces transplantable tumors in mice and the tumors appear, on the average, after about three months. Further experiments may define more exactly the position of the compound in the series, but it is evident from the tests already completed that the hydrocarbon is comparable in carcinogenic activity with cholanthrene and methylcholanthrene. The five-membered ring characteristic of the cholanthrene system is of importance in contributing to the activity of hydrocarbons of this type only in that it includes carbon substituents at the 5- and 10-positions, and the intact ring is by no means essential. The results (Shear, unpublished) obtained with the monomethyl compounds are of further interest. It had been found by the research group in London that 5-methyl-1,2-benzanthracene is slowly, if definitely carcinogenic, and a similar conclusion was reached in experiments with material prepared by a different synthesis. In marked contrast to the behavior of this isomer, 10-methyl-1,2-benzanthracene produced tumors in a large proportion of the mice tested in from three to four months. This compound of simple structure is nearly as active as the cholanthrenes.

When the previous results are viewed in retrospect, substitution at positions 5 and 6 appears to be of secondary importance. While it is true that 5,6-dialkyl-1,2-benzanthracenes regularly exhibit cancer-producing properties and that this fact provided a valuable clue which led to the discovery of carcinogenic activity among the cholanthrenes, the most important structural feature of methylcholanthrene is not the 5,6-substitution, or the presence of an added ring, but simply substitution at the meso-position 10. It is very interesting that 1,2-benzpyrene may be regarded as a 1,2-benzanthracene with a carbon substituent at the alternate meso-position 9, and that 8,9-dimethylene-1,2-benzanthracene,[63] an isomer of cholanthrene, shows some activity (Shear: tumors in 7 mos.). Obviously compounds with still simpler substituents at C_9 merit investigation. That too great an elaboration of an effective type of structure may result in loss of potency has been demonstrated repeatedly, and a further example is that the 7-methyl derivative[62] of 8,9-dimethylene-1,2-benzanthracene is inactive. Particularly striking is the case of 10-isopropyl-1,2-benzanthracene, which was prepared by Cook[31] in 1932. In contrast to the 10-methyl compound, the hydrocarbon was found to be devoid of carcinogenic properties. The substance is somewhat comparable with the rather slowly acting 16,20-dimethylcholanthrene, for this carries a branched-chain substituent at the same meso position.

The discovery of substances far simpler in structure than methylcholanthrene which approach it in carcinogenic potency has a possible bearing on the hypothesis that cancer-producing hydrocarbons may arise in the organism by the abnormal metabolism of cholesterol or of bile acids. Hitherto this hypothesis has found some support not only in the demonstration that bile acids can be transformed by chemical means into methylcholanthrene, but also in the apparently striking circumstance that this particular hydrocarbon, which carries as a mark of its possible origin the cyclopenteno ring characteristic of the sterols and sex hormones, is outstandingly potent in comparison with other compounds. While the possibility of the biological formation of methylcholanthrene remains undisputed, if, to be sure, quite unestablished, the observation that comparable activity is exhibited by simpler hydrocarbons lacking both the C_{20}-methyl group and the cyclopenteno ring characteristic of the sterols, and of a type not likely to arise in the process of metabolism, weakens somewhat the circumstantial evidence favoring acceptance of the hypothesis.

Other Studies (pp. 92-93). The report of A. A. Morton, Clapp and Branch [Ref. 25 and *Am. J. Cancer*, **26**, 754 (1936)] that triphenylbenzene and tetraphenylmethane produce malignant tumors in mice has not yet been confirmed in other laboratories. Shear (*loc. cit.* p. 349, and private communication) obtained entirely negative results with triphenylbenzene. Each of twenty mice received a subcutaneous injection of 10 mg. of a sample of the hydrocarbon which had been purified for an atomic weight determination. No tumors had appeared at the end of sixteen months and there were twelve survivors.

Negative results have been obtained with dehydronorcholene (Cook *et al., loc. cit.*, p. 349, Shear), hexahydromethylcholanthrene (Shear), and dodecahydrocholanthrene (Cook, *et. al.*)

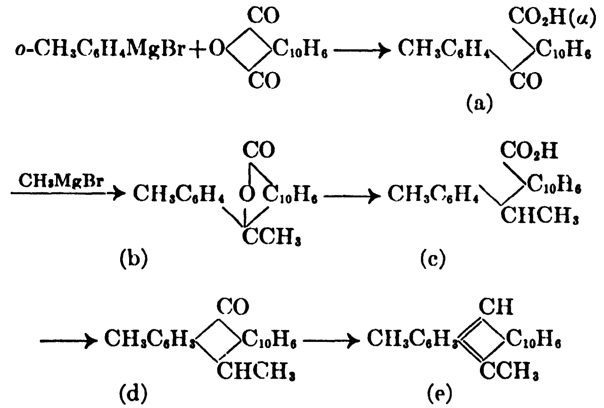
Tumors have been produced by the subcutaneous injection of aqueous solutions of the sodium salts of 1,2,5,6-dibenzanthracene-endo-α,β-succinic acid[18] (Cook, *et. al.*) and of methylcholanthrene-choleic acid[19] (Shear), in the latter case without any difficulty arising from the hemolytic action of uncombined desoxycholic acid. The actions of the former compound are described by Burrows and Cook, *Am. J. Cancer*, **27**, 267 (1936), and by Parsons, *J. Path. Bact.*, **43**, 1 (1936).

Reviewing the extensive literature of the biological studies of carcinogenic agents, Cook, *et al.*, note that "The results obtained in the last few years have shown that a variety of tumors (carcinoma of the skin, kidney, testis, bladder, liver, and uterus; sarcoma of the subcutaneous tissue, peritoneum and spleen) can be induced by pure chemical compounds." References may be found in this review to interesting studies of the rate of disappearance of carcinogenic hydrocarbons in the body, the effect of these compounds on such processes as respiration, the influence of genetic factors, the influence of the medium for the administration, the effect of inhibitors, the propagation of tumors by cell-free material, and other matters. A summary of the results of studies of the action of hormone preparations (pp. 217-219) shows that between thirty and forty instances of mammary cancer in male mice receiving oestrin have been recorded, but that no carcinogenic action truly comparable with that of the benzanthracene hydrocarbons has been observed.

The report of Browning and his collaborators[26] that the styryl quinoline derivative (styryl 430) has cancer-producing properties has been confirmed in further work by Browning, Gulbransen and Niven, *J. Path. Bact.*, **42**, 155 (1936). The interesting discovery of Yoshida (see Cook, *et al.*, for references) that *o*-aminoazotoluene has carcinogenic properties has been confirmed in repeated experiments in various laboratories.

Administered by subcutaneous injection or orally, the substance produces tumors of the liver and bladder. Boyland and Brues (cited by Cook, *et al.*) found that 3,4,5,6-dibenzcarbazole produces proliferation of the bile ducts in a large proportion of cases when applied to the skin of mice. Since this substance may be regarded as a product of the dehydrogenation and condensation of two molecules of β-naphthylamine, the carcinogenic power of the compound is of interest in connection with the cases of bladder cancer found among workers engaged in the manufacture of dyestuff intermediates, particularly β-naphthylamine [Ref. 27, also W. C. Hueper, *J. Ind. Hyg.*, **18,** 140 (1936)].

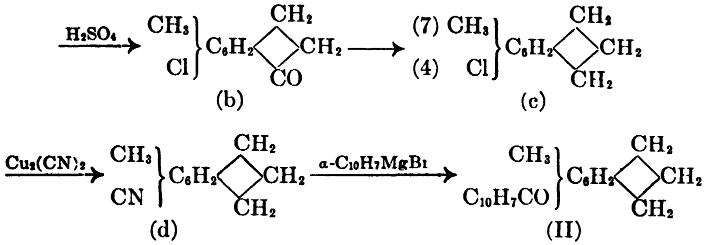
Synthesis of 5,10-Dimethyl-1,2-benzanthracene (addition to p. 94). For the preparation of this actively carcinogenic hydrocarbon and related compounds, Fieser and Newman, *J. Am. Chem. Soc.*, **58,** 2376 (1936), developed a synthesis which combines various features of other methods. As in Cook's synthesis of the 6- and 7-isopropylbenzanthracenes (p. 94), the starting material was 1,2-naphthalic anhydride (previously called 1,2-naphthalene dicarboxylic acid anhydride), a compound which is now readily available by a convenient synthesis (Ref. 8, p. 221). On interaction of the anhydride with *o*-tolylmagnesium bromide, addition occurred



to some extent at each carbonyl group, but the desired *o*-toluyl-α-naphthoic acid (a) was the chief product. 1,2-Naphthalic anhydride is attacked chiefly at the less hindered β-group in both the Friedel and Crafts and the Grignard reactions, but it is only in the latter case that a substituent can be introduced at the ortho (or meta) position of the benzenoid ring. For the introduction of a methyl group, the ester of the keto acid (a) was treated with the Grignard reagent, as in analogous cases in the aliphatic series (p. 72, VII ⟶ VIII), but with only moderately satisfactory results. When the free acid (a) was treated with an excess of methylmagnesium bromide, the lactone (b) was obtained in 86% yield. Reduction of the lactone was accomplished by the Clemmensen method and the acid (c) was cyclized with sulfuric acid to the anthrone (d). Reduction with zinc dust and alkali gave the desired 5,10-dimethyl-1,2-benzanthracene (e). 5-Methyl- and 10-methyl-1,2-benzanthracene were synthesized by obvious variations of the same scheme. 10-methyl-1,2-benzanthracene has been prepared also from 1,2-benz-10-anthrone and methylmagnesium iodide (Fieser and Hershberg, unpublished results). Some reduction occurred in the reaction of the keto acid (a) with Grignard reagents of higher molecular weight.

Synthesis of Methylcholanthrene (pp. 105-106). An improved process for the synthetic preparation of methylcholanthrene and related hydrocarbons has been described by Fieser and Seligman, *J. Am. Chem. Soc.*, **58**, 2482 (1936). 4-Chloro-7-methylhydrindene was employed in place of the 4-bromo compound (corresponding to I) for the preparation of the required ketone (II, p. 106). The hydrindene derivative was obtained by application of the reaction of F. Mayer and P. Müller, *Ber.*, **60**, 2278 (1927), rather than by the Blanc reaction and the malonic ester synthesis.[62] *p*-Chlorotoluene was condensed with β-chloropropionyl chloride by means of aluminum chloride, giving a mixture of the two possible chloroketones (a); cyclization to a hydrindone mixture (b) was accomplished by treatment with concentrated sulfuric acid. Reduction of the mixture afforded a single product, 4-chloro-7-methylhydrindene (c), which was converted into the corresponding nitrile (d) by interaction with cuprous cyanide in pyridine solution (modified Rosenmund-von Braun reaction, yield 78%). Condensation of the nitrile with α-naphthylmagnesium bromide gave the desired ketone II in 89% yield. It is interesting that the yield of the ketone is nearly twice as great as in the condensation of the Grignard reagent from 4-bromo-7-methylhydrindene with α-naphthoyl chloride[62] or with α-naphthonitrile [Bachmann, *J. Org. Chem.*, **1**, 347 (1936)]. The pyrolysis of the ketone pro-

$$p\text{-}CH_3C_6H_4Cl + ClCH_2CH_2COCl \longrightarrow \underset{(a)}{CH_3C_6H_3(Cl)COCH_2CH_2Cl}$$



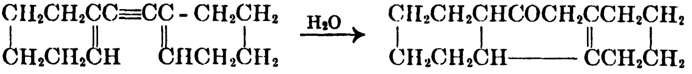
ceeded well on a large scale, giving pure methylcholanthrene in 49% yield. A by-product formed in the pyrolysis was characterized as a hydrocarbon ($C_{21}H_{20}$) and regarded as resulting from the reduction of the carbonyl group of the ketone II. The isolation of products of both reduction and oxidation (anthrones, see p. 108) in the Elbs condensation suggests that a process of disproportionation occurs as a side reaction. By the new synthesis methylcholanthrene can be prepared in quantity in over-all yield of 20% from *p*-chlorotoluene.

Bachmann (*loc. cit.*) reports that in the preparation of 1,2,5,6-dibenzanthracene by the Elbs reaction the yield in the pyrolysis was increased to about 50% by the addition of 10% of zinc dust. This modification does not appear to have been tried in the case of the methylcholanthrene synthesis. Bachmann prepared meso-dihydromethylcholanthrene through the disodium and dilithium compounds.

Synthesis of Phenanthrene and Hydrophenanthrene Derivatives (p. 110). The general interest in phenanthrene derivatives of various types has led to the development of a number of new methods of constructing the phenanthrene ring system. Certain of the methods are appropriately discussed in connection with special fields of investigation, but there are others which as yet have not found sufficient application to any one specific problem to be classified very satisfactorily. The two diene syntheses described on page 110 seem to belong to this class and it is perhaps appropriate to include, in a review of the extensions of these methods, references to certain other phenanthrene syntheses. (Another diene synthesis of polycyclic compounds is described on p. 388.

The diene synthesis of Fieser and Hershberg[73] proved very satisfactory for the preparation of 3-*ter.*-butylphenanthrene [Fieser and Price, *J. Am. Chem. Soc.*, **58**, 1838 (1936)] and of chrysene and 2,3-dimethylchrysene, but attempts to prepare hydrocarbons of the 3,4-benzphenanthrene and 6,7-acechrysene series were successful only in the case of the dimethyl derivatives and then the yields were poor [L. F. Fieser, M. Fieser and Hershberg,[74] *ibid.*, **58**, 1463 (1936)]. Fieser and Holmes, *ibid.*, **58**, 2319 (1936), investigated a variation of the general plan of applying the Diels-Alder reaction to unsaturated cyclic compounds and found that *α,β*-unsaturated esters are capable of entering into the reaction. The addition of dienes to 3,4-dihydro-1-naphthoic ester occurs at a temperature somewhat higher than that required in the case of 3,4-dihydro-1,2-naphthalic anhydride (XI), affording hydrophenanthrene derivatives of a type hitherto inaccessible. Using the morphine numbering system because of the possible application of the results to morphine chemistry, the product obtained from butadiene is 5,8,9,10,13,14-hexahydrophenanthrene-13-carboxylic acid, a substance having a carbon substituent at the position which is indicated as being the most likely point of attachment of the ethanamine chain of morphine (p. 36). In order to provide a closer approach to the morphine type of structure a method was developed for the synthesis of substituted dihydronaphthoic esters. In a typical case anisole is condensed with succinic anhydride and the product is reduced and converted into α-oxalyl-γ-anisylbutyric ester. On hydrolysis with 15% sulfuric acid this is converted into α-keto-δ-anisylvaleric acid, which can be cyclized to 7-methoxy-3,4-dihydro-1-naphthoic acid with 65% sulfuric acid. By condensing the corresponding ester with butadiene, a 3-methoxyhexahydrophenanthrene-13-carboxylic acid was obtained. The methoxyl group occupies the same position as that of codeine (p. 25).

A novel synthesis of hydrophenanthrene derivatives is described by Pinkney, Nesty, Wiley and Marvel, *ibid.*, 58, 972 (1936). The dimagnesium halide of acetylene is condensed with two molecules of cyclohexanone and the resulting acetylenic glycol is dehydrated with 40% sulfuric acid to the dieneyne (a). On treatment with 85% formic acid this undergoes simultaneous hydration and cyclization and yields Δ^{11}-dodecahydrophenanthrone-9 (b). The fully saturated hydrocarbon obtained from this ketone was not dehydrogenated by selenium at 320°.



$$\begin{array}{l} CH_2CH_2CC{\equiv}CC-CH_2CH_2 \\ CH_2CH_2CH \quad CHCH_2CH_2 \end{array} \xrightarrow{H_2O} \begin{array}{l} CH_2CH_2CHCOCH_2CCH_2CH_2 \\ CH_2CH_2CH—CCH_2CH_2 \end{array}$$

(a) (b)

Another scheme for the synthesis of phenanthrenes involves the closing of the central nucleus through acetic derivatives of diphenyl or of a hydrodiphenyl. Chatterjee, *J. Indian Chem. Soc.*, 12, 591 (1935), prepared cyclohexanone-2-acetic ester from 2-carbethoxycyclohexanone by the Reformatsky reaction and hydrolysis, condensed the keto ester with phenylmagnesium bromide, and obtained diphenyl-2-acetic acid by treatment of the carbinol with sulfur, followed by hydrolysis. Cyclization with sulfuric acid gave 9-phenanthrol. Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936), obtained 2-phenylcyclohexanol in almost quantitative yield by the condensation of cyclohexene oxide with phenyllithium. The alcohol was oxidized to 2-phenylcyclohexanone and the $-CH_2CO_2H$ group was introduced by the Reformatsky reaction, dehydration, and hydrogenation. Cyclization with sulfuric acid gave 1,2,3,4,9,10,11,12-octahydrophenanthrone-9, which yielded 9-phenanthrol on dehydrogenation with platinum. On converting 2-phenylcyclohexanol into an acetic acid derivative by the malonic ester synthesis and cyclizing the product, an isomeric octahydrophenanthrene was obtained. Sherwood, Short and Woodcock, *ibid.*, 322 (1936), synthesized 9-phenanthrol by a combination of the procedures of Chatterjee and of Cook and coworkers. Essentially the same method of synthesis, suitably elaborated, was employed by Hewett, *ibid.*, 596 (1936), for the synthesis of 3,4-benzphenanthrene and its 2-methyl derivative.

Short, Stromberg and Wiles, *ibid.*, 319 (1936), have called attention to the interesting observation of Berger, *J. prakt. Chem.*, **133,** 338 (1932), that phenanthrene can be obtained in fair yield by heating 2,2′-dimethyldiphenyl with sulfur at 250°. The English workers found that the carbinol from 2-methylcyclohexanone and *o*-tolylmagnesium iodide yields phenanthrene on similar treatment, but the reaction does not appear to be capable of general application.

Chapter IV

Occurrence of Cholesterol (p. 112). Although the cholesterol present in the brain and gall stones occurs almost exclusively in the free condition, the material found in most organs of the body is present partly as such and partly in the form of fatty acid esters. In a careful investigation of the cholesterol content of blood serum, which normally contains 0.15-0.25 g. of total cholesterol per 100 cc., Sperry, *J. Biol. Chem.*, **114,** 125 (1936), found that the percentage of uncombined cholesterol is even more constant and lower than indicated in previous work. The average found for a number of different individuals was 26.9%, with a standard deviation from the mean of only ±1.4%.

Cholesteryl Esters (p. 112). Nedswedski, *Z. physiol. Chem.*, **236,** 69 (1935); **239,** 165 (1936), observed the enzymatic synthesis of cholesteryl esters in colloidal solutions containing cholesterol, a higher fatty acid (palmitic, stearic, oleic), pancreatic lipase, and bile salts. Ester formation does not occur in the absence of bile salts, which appear to have a stabilizing influence on the enzyme. The salts of cholic, glycocholic, and taurocholic acid seem to be equally effective. The colloidal solutions of cholesterol were prepared by the usual process [Porges and Neubauer, *Biochem. Z.*, **7,** 152 (1908)] of pouring an acetone solution of the sterol into water and evaporating the organic solvent.

Sitosterols (p. 112). Some further progress has been made in characterizing the phytosterol fractions which Anderson[2] designated α-, β-, and γ-sitosterol. From the observation that β-sitosterol and stigmasterol yield the same hydrogenation products, Bengtsson, *Z. physiol. Chem.*, **237,** 46 (1935), concluded that the β-compound has the structure of 22-dihydrostigmasterol. This structure is also suggested for "sitosterol" by Vanghelovici and Angelescu, *Bul. soc. chim. România,* **17,** 177 (1935), who identified acetone as one product of the oxidation of the acetate, indicating that the side chain terminates in $-CH(CH_3)_2$. The most soluble phytosterol fraction from wheat-germ oil, obtained by Anderson only in an impure condition and referred to by him as α-sitosterol, has been investigated further by Wallis and Fernholz, *J. Am. Chem. Soc.,* **58,** **2446** (1936), who succeeded in isolating two new doubly unsaturated sterols in a pure condition. One of these, α_1-sitosterol, is an isomer of stigmasterol ($C_{29}H_{48}O$), while the other (α_2) probably is a homologue, $C_{30}H_{50}O$.

Preparation of Cholesterol (pp. 112-113). A rapid method of extracting cholesterol from brain tissue has been developed by Remesow and Lewaschowa, *Z. physiol. Chem.,* **241,** 81 (1936). After cooling the tissue with liquid air it is possible to grind the material to a fine powder without previous drying, and on extraction with acetone about 83% of the total cholesterol present can be obtained in a satisfactory condition.

Lanosterol (p. 113). In 1872 E. Schulze isolated from the wool fat of sheep a substance which, because it seemed to resemble cholesterol, was called "isocholesterol." Much later it was shown by Windaus and Tschesche, *Z. physiol. Chem.,* **190,** 51 (1930), that "isocholesterol" is a mixture of two substances, lanosterol and agnosterol. The formulas and properties found for these supposed sterols are listed in the table, p. 113. In a later investigation, H. Schulze, *ibid.,* **238,** 35 (1936), dehydrogenated a lanosterol-agnosterol mixture containing 92% of the former compound and identified 1,2,8-trimethylphenanthrene as a product of the selenium treatment. Since alkyl phenanthrenes have been obtained as degradation products of terpenoid compounds such as abietic acid (p. 58) and isoagathic acid (p. 69), but not of sterols, it appears from this evidence and from the empirical formula that lanosterol is a triterpene alcohol (pp. 318-321) and not a sterol. The compound is not altered by being heated with platinum at 300° and therefore all six-membered rings present in the molecule must be protected from ready aromatization by tertiary methyl groups. Previously polyterpenoid compounds had been known to occur only in plants, and it is of interest that the constituents of "isocholesterol" found in wool fat have been found incapable of absorption by the animal organism and consequently they cannot be acquired through foodstuffs. It therefore seems that the animal organism can synthesize polyterpenes as well as sterols. A further characterization of lanosterol has been undertaken by Dorée and Petrow, *J. Chem. Soc.,* **1562** (**1936**).

H. Schulze also investigated the substance **onocerin** from the root of *Ononis spinosa,* previously regarded as a sterol on the basis of a rather fragmentary characterization. On dehydrogenation this was found to give in unusually good yield a hydrocarbon identified as 1,2,5,6-tetramethylnapthalene, a characteristic degradation product of a number of triterpenoid compounds (p. 319). From the analysis of various derivatives, Schulze concluded that the formula of the substance is $C_{30}H_{50}O_2$ $\pm 2H$, and that it is in fact a triterpenoid, diatomic alcohol.

Sterols (p. 113). The isolation from wax of a substance named **bombicesterol,** $C_{27}H_{46}O$, m.p. 139-140°, $[\alpha]_D$ −31.5°, is described by Kawasaki, *J. Pharm. Soc. Japan*, **55,** 758 (1935).

Δ^5-Cholestenone (p. 115). Butenandt and Schmidt-Thomé, *Ber.* **69,** 882 (1936), found that when the oxidation product of cholesterol dibromide is debrominated by short heating with zinc in neutral alcoholic solution the double bond does not migrate to a position of conjugation, and the product is Δ^5-cholestenone (m.p. 127°), an isomer of the ordinary (Δ^4) cholestenone (m.p. 80°). Δ^5-Cholestenone is stable in neutral solutions but rapidly rearranges into the Δ^4-isomer in warm alcohol containing a trace of mineral acid or alkali, or in glacial acetic acid solution. When Δ^5-cholestenone dibromide is debrominated with zinc and acetic acid, with sodium iodide and alcohol, or with zinc and weakly acidic alcohol, the conditions are such as to cause the unsaturated ketone first formed to rearrange in the course of the reaction.

Stereochemistry of the Steroids (addition to p. 117). Callow and F. G. Young, *Proc. Roy. Soc.* (London), **A157,** 194 (1936), have made a preliminary study of the application of van't Hoff's principle of optical superposition to the sterols, bile acids, and other biologically important compounds containing the reduced cyclopentenophenanthrene ring system. The English investigators propose the term "steroid" as a generic name for the entire group of compounds having this common structural unit. On comparing the specific rotations of a number of diastereomeric pairs of compounds of opposite configuration at C_3, it was found that in most cases the contribution of carbon atom 3 to the molecular rotation varies between fairly narrow limits, with a mean value of ±11.5°. The effect of an inversion at C_5 is small and irregular. From a comparison of a number of pairs of compounds such as cholestanone and cholestenone it was established that a 4,5-ethylenic linkage generally causes a marked increase in dextrorotation (av. +220°). The effect of a 5,6-double bond is of about the same magnitude but in the opposite direction (av. −230°). Such simple empirical rules, if confirmed and extended, should provide a useful basis for the criticism of constitutional formulas suggested from chemical considerations.

Rosenheim Reaction (p. 118). According to observations of Schoenheimer and Evans, *J. Biol. Chem.*, **114,** 567 (1936), the Rosenheim color reaction is given by sterols possessing a system of conjugated ethylenic linkages (e.g. ergosterol, scillaridin A) or by those capable of forming such a system by interaction with trichloroacetic acid (e.g. allocholesterol, see p. 361).

Microdetermination of Cholesterol (p. 119). Much attention has been given to the development of rapid and accurate methods for the determination of cholesterol in blood and other biological material. A particularly satisfactory procedure for the determination of free and total cholesterol is that of Schoenheimer and Sperry, *J. Biol. Chem.*, **106,** **745** (1934). Only 0.2 cc. of serum or whole blood is required and small amounts of cholesterol may be determined rapidly and accurately. The sample is extracted with acetone-alcohol and the free cholesterol is precipitated from a portion of the solution with digitonin. Total cholesterol is precipitated similarly from another portion of the extract after alkaline hydrolysis of the cholesteryl esters, and the cholesterol content of the two precipitates is determined by application of a color reaction with acetic anhydride and sulfuric acid, using a sensitive photometer. The accuracy is comparable with that obtainable with the macrogravimetric procedure of Windaus, and the introduction of colorimetry in the final step makes it possible to analyze a sample one one-hundredth the size previously required. The results may differ slightly in some cases because saturated sterols if present are precipitated by digitonin but do not give the color reaction. A modification of the Schoenheimer-Sperry procedure has been developed by C. Riegel and Rose, *ibid.*, **113,** 117 (1936), for the determination of 0.5 to 5 mg. of free and combined cholesterol in bile (1-10 cc.), with an accuracy of ±5%. The initial extraction is made with ether.

In contrast to the colorimetric determination of digitonin precipitates, the direct application of colorimetry does not distinguish between free and combined cholesterol, since the esters give nearly the same color reactions as the sterol itself. Reinhold, *Am. J. Clin. Path.*, **6,** 22, 31 (1936), has shown, however, that by suitable modification of standard colorimetric methods it is possible to obtain results for total cholesterol which agree reasonably well with those of the gravimetric digitonin methods.

An entirely new method of determining both free and combined cholesterol has been introduced by Sobel, Drekter and Natelson, *J. Biol. Chem.*, **115,** 381, 391 (1936). Free cholesterol is precipitated as pyridine cholesteryl sulfate, unchanged esters and lipoids are extracted with petroleum ether, and the amount of cholesterol in the precipitate is estimated by the Liebermann-Burchard reaction. The values for total cholesterol in blood serum determined by the new method were comparable with those obtained by the cholesterol digitonide method, although they generally were slightly higher. The values found for free cholesterol, however, indicated that only 6-10% of the total sterol is present as such, whereas from the results obtained by the cholesterol digitonide methods it has been considered that the percentage is of the order 25-35% (see p. 357. The authors suggest that a part of the cholesterol formerly regarded as free may be present in some labile combination which is split by digitonin but not by the pyridine sulfate reagent.

Cholesterol Digitonide (p. 119). Dissociation into the components can be brought about by boiling a solution of cholesterol digitonide with alcoholic sodium acetate solution. On adding a suitable amount of ether the digitonin and the sodium acetate are precipitated while the cholesterol remains in solution. Lifschütz, *Biochem. Z.*, **282,** 441 (1935).

Isomers of Cholesterol (addition to p. 120). A number of observations have appeared in the literature regarding a substance known as "allocholesterol" (m.p. 117°) which Windaus[29] prepared by the action of potassium acetate on cholesterol hydrochloride and which he regarded as the Δ^4-isomer of cholesterol. It was thought that the substance rearranges easily under the influence of hydrochloric acid into cholesterol (as stated in the first edition, pp. 119, 281-282). Recently these conclusions have been found erroneous. Pure allocholesterol (Δ^4) was prepared for the first time by Schoenheimer and Evans, *J. Biol. Chem.*, **114,** 567 (1936), by application of the general method of Meerwein and R. Schmidt, *Ann.*, **444,** 221 (1925), for the reduction of α,β-unsaturated ketones to the corresponding unsaturated alcohols. Cholestenone, reduced at the carbonyl group with aluminum isopropylate, gave a mixture of the epimeric unsaturated alcohols, **allocholesterol** (m.p. 132°) and ***epi*allocholesterol** (m.p. 84°). The stereoisomers form a molecular compound which is not altered on repeated crystallization, but a separation can be accomplished by precipitating the allocholesterol with digitonin. The pure sterol recovered by the pyridine-ether method (p. 119) differed in properties from Windaus' "allocholesterol," and the latter substance was found on further investigation to be a mixture of allocholesterol and cholesterol. Pure allocholesterol does not rearrange to cholesterol in the presence of hydrochloric acid, but it does undergo dehydration to a hydrocarbon. The cholesterol obtained in the early experiments was that already present in the mixture, the dehydration of the isomeric sterol facilitating its isolation. In a later investigation Evans and Schoenheimer, *J. Biol. Chem.*, **115,** 17 (1936), showed that another supposed isomer known as "β-cholesterol" is in reality a molecular compound containing equal parts of dihydrocholesterol and *epi*allocholesterol. The former substance is removed by precipitation with digitonin.

Both allocholesterol and *epi*allocholesterol suffer dehydration with remarkable ease, the reactions proceeding nearly quantitatively on refluxing for two hours solutions of the sterols in 95% alcohol approximately *N*/30 in hydrogen chloride. The theoretical significance of the reaction is discussed on page 282, at least for the case of the *epi*-compound which alone was mentioned in the first account of the work. It now appears that the facile dehydration is characteristic of both α,β-unsaturated alcohols, regardless of the spatial arrangement of the hydroxyl group. The same substance, a doubly unsaturated hydrocarbon melting at 79° and giving a positive Rosenheim reaction, is formed in each case. Schoenheimer and Evans ascribe to the hydrocarbon the $\Delta^{2,4}$-structure indicated in formula XIX, p. 282, but this appears inconsistent with the absorption spectrum of the compound, which shows maxima at 229, 235, and 240 mμ. The selective absorption, like the color reaction, shows that the two double bonds are conjugated, but if they were contained in the same ring there should be a greater resemblance to the hydrocarbons ergostatriene ($\Delta^{5,7,22}$) and 7-dehydrocholestene, which show maxima at longer wavelengths (273, 280 mμ). The spectrum of the hydrocarbon in question is indicative rather of a conjugated system distributed between two rings (see the work of Callow, p. 374). Consequently it is suggested that the hydrocarbon has the $\Delta^{3,5}$-structure and that it is formed by the 1,4-elimination of water from the unsaturated alcohol:

$$-\underset{3}{C}H(OH)\underset{4}{C}H{=}\underset{5}{C}\underset{6}{C}H_2- \xrightarrow{-H_2O} -\underset{3}{C}H{=}\underset{4}{C}H\underset{5}{\dot{C}}{=}\underset{6}{C}H-$$

The hydrocarbon of Schoenheimer and Evans resembles cholesterylene, m.p. 78-79°, but it appears to be an isomer of this compound. Cholesterylene, was first described by Mauthner and Suida, *Monatsh*, **17**, 2 (**1896**), and is prepared by dehydrating cholesterol with anhydrous coppe sulfate at 200° or by heating cholesteryl choride with quinoline. It show selective absorption in the ultraviolet region with maxima at 294, 304, an 321 mμ [Heilbron, R. A. Morton and Sexton, *J. Chem. Soc.*, 47 (1928)] In analogy with ergostatriene and 7-dehydrocholestene, it seems likel that the double bonds of cholesterylene are located in a single ring possibly at the 2,3- and 4,5-positions. The dehydration at an elevate temperature would then involve the elimination of the hydroxyl grou with a C_2-hydrogen atom, and migration of the C_5-C_6 double linkage to a position of conjugation in ring A.

***Epi*cholesterol** is a second isomer of the natural sterol which has been characterized recently. The compound (m.p. 141°) was prepared by Marker, Oakwood and Crooks, *J. Am. Chem. Soc.*, **58**, 481 (1936), by passing oxygen into a solution of the Grignard reagent obtained from cholesteryl chloride. This gave a mixture of *epi*cholesterol and cholesterol, from which the cholesterol was removed by precipitation with digitonin. For the preparation of the new sterol in quantity a partial separation is made by crystallization of the acetates, giving a product containing 80-90% of *epi*cholesterol, and the remaining cholesterol is removed by crystallization of the benzoates [Marker, O. Kamm, Oakwood and Laucius, *ibid.*, **58,** 1948 (1936)]. *Epi*cholesterol was obtained in still another way by Marker, O. Kamm, Fleming, Popkin and Wittle, *J. Am. Chem. Soc.*, Paper X, in press. On oxidation with chromic anhydride, cholesteryl chloride gave 7-ketocholesteryl chloride, the latter was converted by potassium acetate in part into 7-keto*epi*cholesterol as the acetate, and reduction by the Wolff-Kishner method afforded *epi*cholesterol. Ruzicka and Goldberg, *Helv. Chim. Acta*, **19,** 1407 (1936), found that *epi*cholesterol is formed along with cholesterol on partially hydrogenating Δ^5-cholestenone in the presence of Raney-nickel catalyst. A separation is accomplished as above, and the process affords a convenient method of preparing the epimer.

Marker and co-workers found that when *epi*cholesterol is heated for sixteen hours in an alcoholic solution which is about 1 *N* in hydrogen chloride the substance is at least partially dehydrated to cholesterylene. The conditions are considerably more drastic than those under which the allo-compounds can be dehydrated, and it is questionable whether epimerization of the hydroxyl group has an appreciable influence on the ease of reaction.

Isomeric ethers and acetates of cholesterol have been investigated with interesting results. Stoll, *Z. physiol. Chem.*, **207,** 147 (1932), observed that when cholesteryl *p*-toluene sulfonate is boiled with methanol it is converted into a methyl ether (m.p. 84°) which, since it is levorotatory like cholesterol, may be called the normal ether. Stoll discovered, however, that when the reaction is carried out in the presence of potassium acetate the product is an isomeric, dextrorotatory, abnormal ether, m.p. 79°. Other alcohols gave similar pairs of isomers. Similarly, Wagner-Jauregg and L. Werner, *ibid.*, **213,** 119 (1932), found that cholesteryl chloride or bromide yields the normal ether when heated with methanol alone at 125°, but gives the abnormal ether in the presence of potassium acetate. They further found that the abnormal ether is converted into the normal compound when it is heated with hydrogen chloride and methanol, and they suggested that in the formation of ethers from cholesteryl halides or from the *p*-toluenesulfonate the abnormal ether is the primary product under all conditions and subsequently rearranges to the normal ether under the influence of liberated acid unless this is neutralized by potassium acetate. While Stoll was of the opinion that the abnormal ether is an *epi*-compound, this conclusion seemed questionable to Wagner-Jauregg and Werner, for on hydrogenating the compound they found that although the reaction did not proceed smoothly, a small amount of normal dihydrocholesteryl methyl ether could be isolated.

More recently Beynon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936), studied the hydrolysis of the two series of cholesteryl ethers with the idea that the abnormal ethers might be derivatives of *epi*cholesterol and might provide a convenient route to this sterol. They found that whereas the normal ethers do not react with halogen acids in acetic acid solution at room temperature the abnormal ethers are converted easily under these conditions into the normal cholesteryl halide (chloride, bromide, or iodide). The English investigators provisionally regarded the isomers which are subject to this facile replacement of the alkoxyl group as ethers of *epi*cholesterol. The inference, however, is far from secure and it appears particularly questionable in the light of the observations of Wallis, Fernholz and Gephart, *J. Am. Chem. Soc.*, **59,** 137 (1937), concerning an isomer of cholesteryl acetate which was obtained by the action of anhydrous potassium acetate on cholesteryl *p*-toluenesulfonate in acetic anhydride solution. Like the abnormal ethers, the new acetate is dextrorotatory, and on hydrolysis it yields an isomer of cholesterol, ***i*-cholesterol** (m.p. 74-75°), which is quite different from the epimer of the natural sterol and from the other two isomers described above. *i*-Cholesteryl acetate does not react with perbenzoic acid or with bromine and shows considerable stability to catalytic hydrogenation, although under special conditions of hydrogenation in glacial acetic acid with Adams' catalyst it yields the normal dihydrocholesteryl acetate. From these observations, Wallis, Fernholz and Gephart conclude that the acetolysis of cholesteryl *p*-toluenesulfonate is accompanied by a molecular rearrangement, and that a rearrangement in the reverse direction occurs in the hydrogenation reaction. They suggest that the rearrangement may be of the type commonly encountered in terpene chemistry and that *i*-cholesterol may contain, in place of a double linkage, a bridge bond extending from C_3 to C_5, with the hydroxyl group situated at C_6. Because of the evident analogies, they suggest that the abnormal ethers of Stoll may be of the same type.

Sterols of Lower Animals (pp. 121-122). A further indication that lower animal organisms utilize sterols derived from their food, rather than synthesize cholesterol, is furnished by the work of Klenk and Diebold, *Z. physiol. Chem.*, **236,** 141 (1935), who isolated from sea anemone (*Anemonia sulcata*) a new sterol of the composition $C_{27}H_{44}O$. This substance, to which the name **actiniasterol** has been given, is doubly unsaturated and possibly is a dehydrogenation product of cholesterol derived by the anemone (carniverous) from the food. The case is parallel to that of the doubly unsaturated oestriasterol, which appears to be produced in the oyster from a phytosterol of the diet.

Sterols in Bacteria (addition to p. 122). A number of attempts have been made to determine if sterols are present in bacteria or only in more highly organized forms of life, such as yeast, and the conclusion usually has been in the negative. Although Hecht, *Z. physiol. Chem.*, **231,** 29, 279 (1935), reported the detection of sterols in tubercular bacilli, it appears from the observations of R. J. Anderson, Schoenheimer, Crowder and Stodola, *ibid.*, **237,** 40 (1935), that all sources of contamination were not eliminated. In more recent work, however, Sifferd and R. J. Anderson, *ibid.*, **239,** 270 (1936), isolated from the unsaponifiable portion of the fat of *Azotobacter chroöcoccum*, which had been cultivated on a scrupulously pure medium containing sterol-free glucose as the only organic constituent, a substance definitely characterized as a mixture of sterols (m.p. 156-158°). The substance constituted no less than 0.13% of the fat and the color reactions resembled those of cholesterol. The evidence clearly indicates that the organism in question is capable of effecting a sterol synthesis from sterol-free food.

Fucosterol (p. 122). Coffey, Heilbron and Spring, *J. Chem. Soc.*, 738 (1936), confirmed the identity of fucostanol and stigmastanol and established the presence of a double bond at C_5-C_6 in *α*-dihydrofucosterol, one of two dihydro derivatives obtained by the hydrogenation of fucosteryl acetate.

Unsaturated Bile Acids (p. 124). The dehydration of most of the known hydroxycholanic acids theoretically can proceed in two directions, giving rise to a mixture of isomeric cholenic acids. Wieland, Kraus, Keller and Ottawa, *Z. physiol. Chem.*, **241,** 47 (1936), found that mixtures indeed result on the thermal dehydration of the 3-, 6-, and 7-hydroxy acids, and they undertook the isolation of the components of these mixtures as pure individuals through the dibromides. In characterizing the products, use was made of the reaction with selenium dioxide, a reagent which, when shaken with a solution of a cholenic acid in chloroform and acetic anhydride, was found to bring about the transformation of $>C{=}CHCH_2—$ into $>C{=}CHCH(OH)—$. Apparently the reagent sometimes acts in a different manner when employed in aqueous alcoholic solution (p. 373), for $>CH\overset{|}{C}{=}\overset{|}{C}CH<$ is converted into $>C{=}\overset{|}{C}—\overset{|}{C}{=}C<$ in the aqueous solvent but remains unchanged when the experiment is conducted under anhydrous conditions (see also p. 369). In chloroform-acetic anhydride solution, the occurrence of a reaction was regarded as a good indication of the presence of an activated methylene group, but unfortunately the structure of the resulting hydroxy compound does not follow without question, for by an allylic shift the system >C=CHCH(OH)— may change to >C(OH)CH=CH— in the course of the reaction. Hydrogenation, resulting in the formation of cholanic acid, *allo*cholanic acid, or both, afforded a means of recognizing a double bond extending to the 5-position.

From the results of the investigation, Wieland came to the following, necessarily qualified, conclusions. Lithocholic acid on dehydration yields chiefly Δ^2-cholenic acid, along with some of the Δ^3-isomer. The elimination of water from 6-hydroxy*allo*cholanic acid gave Δ^5-cholenic acid as the chief product, along with some of the Δ^6-acid, while 7-hydroxycholanic acid yielded a mixture of Δ^6- and Δ^7-cholenic acids in which the former predominated. From desoxycholic acid there was obtained as the chief product a substance which probably is $\Delta^{2,11}$-choladienic acid.

In the course of the work attempts were made to aromatize either ring A or ring B by the pyrolysis of the hydroxycholenic acids obtained in the oxidations with selenium dioxide. Theoretically such a reaction might occur, with the elimination of water and methane, but the results were entirely negative. The angular methyl group at C_{10} evidently renders the aromatization very difficult (see p. 254).

Determination of Bile Acids (p. 125). Doubilet, *J. Biol. Chem.*, **114,** 289 (1936), developed methods for the analysis of bile for glyco- and tauro-bile acids, for total and conjugated bile acids, and for cholic and desoxycholic acids. In a typical case, bile from a human gall bladder was found to contain 7.6% of total bile acids, of which 3.3% was cholic acid and 4.3% desoxycholic acid. Of the total acids 20% was found to occur free, 46% was conjugated with glycine, and 34% was conjugated with taurine.

Ursodesoxycholic Acid (p. 126). Iwasaki, *Z. physiol. Chem.*, **244,** 181 (1936), found the supposed "ursocholanic acid"[63] to be identical with cholanic acid and proved that ursodesoxycholic acid has the same structure as chenodesoxycholic acid and differs from this substance only in the configuration at C_7.

Acids from Toad Bile (p. 128). Shimizu and Oda[69] oxidized trihydroxybufosterocholenic acid to a triketo acid and eliminated the oxygen atoms by reduction according to Clemmensen. The resulting bufosterocholenic acid formed a bromolactone on reaction with bromine, suggesting that the double bond is located in the side chain, probably in the β,γ- or γ,δ-position. Shimizu and Kazuno, *Z. physiol. Chem.*, **239,** 74 (1936), carried the investigation a step further by oxidizing bufosterocholenic acid with ozone or with chromic anhydride. The chief product of the reaction was identified as bisnorcholanic acid (p. 146), an observation which proves that the ring system is that of the other natural bile acids and that a double bond is located in the side chain at C_{22}-C_{23}, as in ergosterol. Shimizu and Kazuno suggest that the remainder of the side chain skeleton may also conform to that of ergosterol: $-CH(CH_3)CH=CHCH(CH_3)CH(CH_3)CO_2H$. The three hydroxyl groups of the acid from toad bile were shown to be located at positions 3, 7, and 12 by the ozone oxidation of the acid to a trihydroxybisnorcholanic acid identical with that obtained by the systematic degradation of cholic acid [*Idem, ibid.*, **244,** 167 (1936)]

A second acid isolated by Shimizu and Kazuno, *ibid.*, **239,** 67 (1936), from the winter bile of the toad is given the name **trihydroxyisosterocholenic acid** (m.p. 227°) and regarded as an isomer of trihydroxybufosterocholenic acid of the formula $C_{28}H_{46}O_5$. The two acids yield different saturated acids on removal of the hydroxyl groups and hydrogenation.

Acids from Rabbit Bile (p. 128). From this source Kishi, *Z. physiol. Chem.*, **238,** 210 (1936), isolated lithocholic acid and two new isomers of desoxycholic acid ($C_{24}H_{40}O_4$). One of these substances, **α-lagodesoxycholic acid** (Gr. *lagōs*, hare), m.p. 156-157°, yielded a hydroxyl-free saturated acid identified as cholanic acid, and on oxidation it was converted into dehydrodesoxycholic acid (3,12-diketocholanic acid). The new acid therefore conforms to desoxycholic acid in the location of the hydroxyl groups and in the configuration of the ring system, and it must differ from this compound only in the steric arrangement of one or both of the hydroxyl groups. As the substance resembles the other bile acids in not being precipitated by digitonin, the configuration at C_3 probably is the same as in desoxycholic acid (*epi*) while that at C_{12} is different. It is very interesting that this subtle difference apparently renders the new acid incapable of sharing with desoxycholic acid the specific property of forming choleic acids (p. 129).

The second new substance **β-lagodesoxycholic acid** (m.p. 213°), yields on oxidation an acid not identical with the known 3,12-, 3,7-, or 7,12-diketo acids and the structure is still unknown.

New Acid from Ox Bile (p. 128). In continuing the systematic working of large quantities of ox bile, Wieland and Hanke, *Z. physiol. Chem.*, **241,** 93 (1936), isolated a substance of exceedingly weak acidity, to which the provisional formula $C_{29}H_{46}O_3$ is assigned. The new compound clearly is of a type quite different from the cholanic acid derivatives and it shows a marked similarity to the acidic triterpenoid sapogenins (pp. 318-321). For this reason it is named **sapocholic acid.** A particularly close resemblance was noted to pyroquinovic acid ($C_{29}H_{46}O_3$), a decarboxylation product of the dibasic quinovic acid (p. 424). Like the sapogenins, sapocholic acid forms a water-insoluble sodium salt, it yields a bromo lactone (γ, δ-unsaturated acid group), and the ester, prepared with the use of diazomethane, is very resistant to hydrolysis.

Bile of the Alligator Turtle (p. 128). Yamasaki and Yuuki, *Z. physiol. Chem.*, **244,** 173 (1936), isolated from this source a trihydroxysterocholanic acid lactone (C_{27} or C_{28}) and a tetrahydroxy lactone (C_{28} or C_{29}).

"Choleic Acid Principle" (p. 131). A further indication that molecular compound formation plays no part in the intestinal digestion of fats or in the transportation of cholesterol in the bile is furnished by the work of Cortese and Bauman, *J. Biol. Chem.*, **113,** 779 (1936). These investigators prepared pure glycodesoxycholic acid by a process similar to that employed for the synthetic conjugation of cholic acid and glycine (p. 125) and found that the conjugated acid, unlike desoxycholic acid itself, does not form true coördinative complexes with fatty acids. Substances described in the literature as more or less stable "glycocholeic acids" are regarded by Cortese and Bauman as impure specimens of the conjugated acid. In the course of the work it was noted that desoxycholic acid loses its power to form choleic acids when the hydroxyl groups are formylated or when the acid is esterified.

Choleic Acids (p. 132). Marx and Sobotka, *J. Org. Chem.*, **1,** 275 (1936), prepared the tetra-choleic acid of anthracene in alcohol-benzene solution. The cis-trans isomers oleic acid and elaidic acid have the same coördination number (8) as stearic acid. Colored choleic acids were prepared from certain colored diketones.

Apocholic Acid and Dihydroxycholenic Acid (p. 132). From the results of a study of the action of selenium dioxide in aqueous alcohol on apocholic acid and in analogy with the behavior of the isomeric ergostenols (p. 371), Callow, *J. Chem. Soc.*, 462 (1936), concluded that the formulas ascribed to the unsaturated acids derived from cholic acid require revision.

Callow considers that in 3,12-dihydroxycholenic acid the double bond probably is located at C_{14}-C_{15} in ring D. This affords a satisfactory interpretation of the oxidative degradation observed by Wieland and Dane,[88] and it accords better with the observation that the acid is susceptible to hydrogenation. In analogy with β-ergostenol, it would be expected that an acid having the $\Delta^{7,8}$-constitution originally attributed to dihydroxycholenic acid would undergo isomerization (to apocholic acid) and not hydrogenation. Apocholic acid, according to Callow, is a $\Delta^{8,14}$-compound similar to α-ergostenol, which likewise is resistant to hydrogenation. The interconversion of apocholic acid and dihydroxycholenic acid (probably an equilibrium) is assumed to involve the migration of the double bond between adjacent positions in rings C and D, and the inert character of this linkage in the case of apocholic acid is attributed to its situation between quaternary carbon atoms (8,14). Wieland, Dietz and Ottawa, *Z. physiol. Chem.*, **244,** 194 (1936), share this view of the structures.

The formula suggested for apocholic acid is supported by the results of a study of the further dehydrogenation of this substance with perbenzoic acid and with selenium dioxide. Isomeric dihydroxycholadienic acids were obtained. The relationships between these substances and their properties, together with the structures which Callow has ascribed to them, are as follows:

$$\begin{tikzcd}
\begin{array}{c}\alpha\text{-Apocholic acid}\\ \Delta{:}8,14\end{array} \arrow[r, shift left, "C_6H_5CO_3H"] \arrow[dr, "SeO_2"] & \begin{array}{c}\alpha\text{-Dihydroxycholadienic acid}\\ \Delta{:}7,8;14,15\ \text{Abs. max. 240-250 m}\mu\end{array} \arrow[l, shift left, "H_2, Pd"] \\
\begin{array}{c}\beta\text{-Apocholic acid}\\ \Delta{:}8,14\end{array} & \begin{array}{c}\beta\text{-Dihydroxycholadienic acid}\\ \Delta{:}9,8;14,15]\ \text{Abs. max. 249 m}\mu\end{array} \arrow[l, "H_2, Pd"']
\end{tikzcd}$$

The type of absorption spectrum exhibited by the doubly unsaturated acids is characteristic of compounds having two conjugated double bonds distributed between two rings (compare the isomers of ergosterol, p. 374. It is of interest that a substance obtained by the action of alcoholic potassium hydroxide on 5,6-dibromocholanic acid and assigned the structure of $\Delta^{4,6}$-choladienic acid conforms to the same rule and exhibits an absorption maximum at about 235 mμ [Wieland and co-workers, *Z. physiol. Chem.*, **241,** 47 (1936)]. β-Apocholic acid appears to be a stereoisomer of ordinary (α-) apocholic acid and to differ from this substance only in the configuration at the asymmetric center C_9. Like the α-acid, β-apocholic acid forms stable molecular compounds with acetic acid and with xylene.

Partial Synthesis of Sterol Derivatives from Bile Acids (p. 136). Employing the method of Wieland and Jacobi,[94] who succeeded in preparing coprostane from cholanic acid by a series of reactions beginning with the condensation of the ester of the bile acid with isopropylmagnesium bromide, Reindel and Niederländer, *Ann.*, **522,** 218 (1936), attempted to prepare a C_{27}-sterol (*epi*coprostanol) from lithocholic acid. They were unable, however, to effect the reduction of an intermediate ketone, 3-*epi*hydroxycoprostanone-24. Sterols with shorter side chains were obtained without difficulty. Using a variation of the general Grignard synthesis, Fernholz, *Ber.*, **69,** 1792 (1936), prepared from cholanic acid a substance having the carbon skeleton of pseudoergostane and apparently consisting in large part at least of the parent hydrocarbon from ergosterol.

Lithocholic Acid from Cholesterol (addition to p. 157). The preparation of a natural bile acid from cholesterol was accomplished for the first time by Schoenheimer and Berliner, *J. Biol. Chem.*, **115,** 19 (1936), the actual starting material being 3-hydroxy-Δ^5-cholenic acid, a substance obtained as a by-product in the preparation of dehydroisoandrosterone as described on page 234 (see also p. 393). This was oxidized to 3-keto-Δ^4-cholenic acid, which on hydrogenation (as the ester) gave a mixture of lithocholic acid and β-3-hydroxy*allo*cholanic acid (p. 170). The mixture was separated by precipitating the latter compound (as the ester) with digitonin. Lithocholic acid is an *epi*-compound and is non-precipitable (p. 231).

Ruzicka's Hydrocarbon "$C_{21}H_{16}$" (p. 158). The hydrocarbon, m.p. 275°, which Ruzicka[44,47] isolated as one product of the dehydrogenation of cholic acid at 360°, has been identified as 5-methyl-2′,1′-naphtho-1, 2-fluorene by Bachmann, Cook, Hewett and Iball, *J. Chem. Soc.*, 54 (1936). Cook and co-workers[50] had been led to suspect this type of structure from spectroscopic studies, and their suggested revision of the formula to $C_{22}H_{16}$ was supported by X-ray crystallographic evidence.[62] In the work cited, five methylnapthofluorenes were synthesized for comparison (Bogert-Cook method) and the 5-isomer was found to be identical with Ruzicka's hydrocarbon. The structure of the compound corresponds to that illustrated in formula II, p. 166, except that the isopropyl group is not present. The low temperature dehydrogenation involves a simple cyclization of the cholic acid side chain at the 16-position without disturbance of any of the carbon atoms other than those of the angular methyl groups.

Dehydrogenation of Hydrindenes (p. 159). Nenitzescu and Cioranescu, *Ber.*, **69,** 1040 (1936), obtained small amounts of naphthalene on passing 1-methylhydrindene and its hexahydro derivative over palladium charcoal at 310-350°, that is, at a temperature considerably below that at which Ruzicka and Peyer[48] observed a reaction. That ring-enlargement can occur under such mild conditions emphasizes the uncertainty in structural evidence based solely upon the results of dehydrogenation. The reaction affords some analogy for the conversion of sterol derivatives into chrysene.

Formation of Spirans (p. 162). E. Bergmann and Blum-Bergmann, *J. Am. Chem. Soc.*, **58,** 1678 (1936), encountered spirans and their rearrangement products in the synthesis of cyclopentenotriphenylene by the Bogert-Cook method.

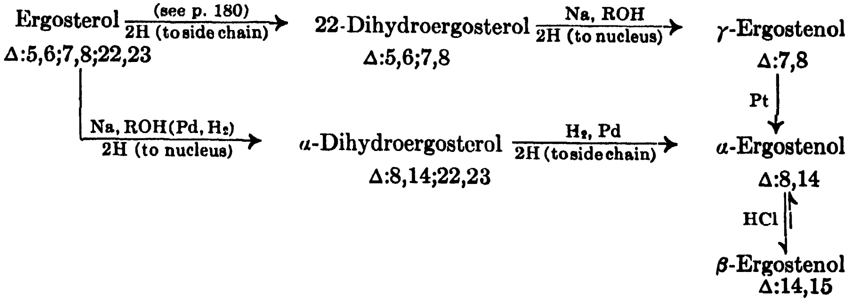
The Diels Hydrocarbon (p. 165). In a further study, Hillemann, *Ber.*, **69,** 2610 (1936), reported that the highly purified compound (126-127°) is not fluorescent.

Mechanism of Dehydrogenation (p. 166). In order to test the theory that the migration of the methyl group at C_{13} has nothing to do with the process of dehydrogenation but is due to the pyrolytic fission of the side chain at C_{17}, E. Bergmann and F. Bergmann, *Chemistry and Industry,* **55,** 272 (1936) reinvestigated the thermal decomposition of cholesteryl chloride at 300° [Mauthner and Suida, *Monatsh.*, **17,** 41 (1896); H. Fischer and Treibs, *Ann.*, **446,** 241 (1926)]. The preliminary results support the above theory, for there was obtained a mobile distillate composed of octane and octene, corresponding to the side chain, and a main fraction from the residue having the composition of a saturated hydrocarbon, $C_{19}H_{30}$, corresponding to the actiocholane part of the molecule.

The Methyl Group at C_{13} (p. 169). A rigid proof of this feature of the structure is provided by observations made in the investigation of the sex hormones, as summarized on page 387.

Ergosterol, Absorption Spectrum (p. 173). From an examination of substances having the same arrangement of conjugated double bonds as ergosterol but lacking the hydroxyl group, Dimroth and Trautmann, *Ber.*, **69,** 669 (1936), found that the conjugated system of the sterol alone is responsible for the characteristic absorption bands between 260 and 290 mμ and that the hydroxyl group is without influence. The compounds examined, ergostatriene ($\Delta^{5,7,22}$) and 7-dehydrocholestene, exhibited the same type of spectrum as ergosterol, showing maxima at approximately 273 and 280 mμ. The first hydrocarbon was prepared by adding maleic anhydride to ergosterol to protect the conjugated system, oxidizing the secondary hydroxyl group of the addition product, reducing the carbonyl group by the Clemmensen method, and eliminating maleic anhydride by vacuum distillation. 7-Dehydrocholestene was obtained from 7-hydroxycholestene [Windaus, *ibid.*, **53,** 495 (1920)] by the method given on page 180 for the preparation of 7-dehydrocholesterol.

Ergostenols (addition to p. 176). By various direct and indirect methods ergosterol has been converted into three well-characterized, singly unsaturated alcohols known as α-, β-, and γ-ergostenol. Since these isomers differ considerably in their stability and in their deportment under hydrogenating conditions, it is a matter of considerable interest to be able to interpret the properties in terms of specific structures. This problem has been solved in the case of β-ergostenol, and the structures suggested for the other isomers are supported by convincing, if not final, evidence. These structures are indicated in the accompanying chart, which summarizes the methods by which the three ergostenols have been obtained.



22-Dihydroergosterol is prepared by protecting the unsaturated system by the addition of maleic anhydride and saturating the double bond in the side chain, as described on page 180, and it appears that the reduction of the substance with sodium and alcohol to γ-ergostenol involves the addition of hydrogen to the 5,6-position, leaving the 7,8-ethylenic linkage undisturbed [Windaus and Langer, *Ann.*, **508,** 105 (1934)]. In the presence of platinum or palladium catalyst, γ-ergostenol fails to absorb hydrogen but is merely isomerized to α-ergostenol, a transformation which is interpreted as involving a migration of the double bond from the 7,8- to the adjacent 8,14-position. α-Ergostenol cannot be hydrogenated under ordinary conditions and it is believed that the inert character of the double bond is due to its location between two quaternary carbon atoms, or bridge heads. A shorter route to α-ergostenol consists in the reduction of ergosterol with sodium and alcohol to α-dihydroergosterol, followed by catalytic hydrogenation of the ethylenic linkage in the side chain [Reindel and E. Walter, *Ann.*, **460,** 214 (1928)]. In the course of the reactions it appears that a nuclear double bond migrates from C_7-C_8 to C_8-C_{14}, and since α-dihydroergosterol can be obtained from ergosterol by catalytic hydrogenation [Heilbron and Sexton, *J. Chem. Soc.*, 924 (1929)] as well as with sodium and alcohol, it is probable that the migration occurs in the first step and is not caused by the catalyst employed in the addition of the second mole of hydrogen.

By the action of hydrochloric acid α-ergostenol is isomerized partially to the third compound, β-ergostenol [Reindel, E. Walter and Rauch, *Ann.*, **452,** 34 (1927); Reindel and E. Walter, *loc. cit.*; Heilbron and Wilkinson, *J. Chem. Soc.*, 1708 (1932)]. It is supposed that the isomerization consists in the migration of the double bond from C_8-C_{14} to the adjacent position C_{14}-C_{15} in ring D, probably by the addition and elimination of hydrogen chloride. The β-compound is the only one of the isomers which is easily hydrogenated. That the double bond of β-ergostenol occupies the position indicated has been established with certainty. Achtermann, *Z. physiol. Chem.*, **225,** 141 (1934), ozonized the acetate (cleavage at C_{14}-C_{15}) and on pyrolysis of the product obtained a keto alcohol of the formula $C_{16}H_{26}O_2$. Laucht, *ibid.*, **237,** 236 (1935), fully characterized this substance by converting it by dehydrogenation with selenium into 2-methylphenanthrene, and he also isolated (as the semicarbazone) the other fragment of the pyrolysis, an α,β-unsaturated aldehyde, $C_{12}H_{22}O$. These products can arise only from an initial ozonolysis between positions 14 and 15.

The structures of α- and γ-ergostenol are not known with equal certainty. From the ready isomerization from the γ- to the α- to the β-form it is inferred that at each step the double bond migrates to an adjacent position, progressing from ring B to ring C, and finally to ring D.

It is of interest that on the introduction of a second nuclear double bond by treatment with perbenzoic acid, α-ergostenol [Windaus and Lüttringhaus, *Ann.*, **481,** 119 (1930)] and β-ergostenol [Morrison and Simpson, *J. Chem. Soc.*, 1710 (1932)] both yield the same compound, dehydroergostenol. The identical substance results from the isomerization of 22-dihydroergosterol with gaseous hydrogen chloride [Windaus and Langer, *loc. cit.*] Dehydroergostenol was obtained by Callow, *J. Chem. Soc.*, 462 (1936), by the action of selenium dioxide on α-ergostenol. Considering the analogy with other dehydrogenation products, Callow suggested that the double bonds occupy the conjugated positions C_8-C_9 and C_{14}-C_{15}. It is interesting that in aqueous alcoholic solution the action of selenium dioxide on sterols having one nuclear ethylenic linkage results in the introduction of an additional double bond [see also Callow and Rosenheim, *ibid.*, 387 (1933)], the reaction apparently involving the 1,4-elimination of two atoms of hydrogen. In the case of ergosterol, dehydrogenation with selenium dioxide in aqueous alcoholic solution results in the extension of the conjugated system already present, the chief product being dehydroergosterol (p. 175).

Isomers of Ergosterol (addition to p. 176). In the course of the work cited above, Callow and Rosenheim noted that α-dihydroergosterol is converted by selenium dioxide into ergosterol-D, an isomer of ergosterol which had been obtained previously from the same starting material using mercuric acetate [Heilbron, Johnstone and Spring, *J. Chem. Soc.*, 2248 (1929)], and by the reduction of a ketone prepared by heating ergosterol with nickel catalyst at 220° [Windaus and Auhagen, *Ann.*, **472,** 185 (1929)]. Callow (*loc. cit.*) suggested for ergosterol-D a formula similar to that assigned to dehydroergostenol, namely, with the nuclear double bonds at the 8,9- and 14,15-positions (and with a third ethylenic linkage in the side chain). This suggestion is based partly upon the fact that ergosterol-D has an absorption maximum at 242 mμ, which is regarded as characteristic of compounds having two conjugated double bonds distributed between two rings. Ergosterol-B_3, another well-characterized isomer which can be obtained (along with the B-, and B_2-compounds) by the isomerization of ergosterol with hydrogen chloride [Windaus, Dithmar, Murke and Suckfüll, *Ann.*, **488**, 91 (1931], is regarded by both Laucht and Callow (*loc. cit.*) as having the bond structure Δ: 7,8; 14,15; 22,23. The sterol adds maleic anhydride. The suggested structure, indicating the presence of conjugated nuclear double bonds distributed between rings B and D, is consistent with the absorption spectrum (maximum at 242 mμ), which is similar to that of the isomer. The presence of two conjugated ethylenic linkages in a single ring has an enhancing effect and the selective absorption occurs at a longer wave length. Ergosterol, 22-dihydroergosterol, and 7-dehydrocholesterol exhibit absorption maxima at about 280 mμ. The marked difference in the absorption spectra of compounds containing the two types of diene systems should be of great value in establishing the structures of other unsaturated compounds.

Ergosterol-D and ergosterol-B_3 are the most fully characterized of a large number of isomers of ergosterol which have been obtained by chemical means. The study of the chemical isomerization was undertaken at a time when it seemed possible to produce in this way substances of the type formed in the process of irradiation (p. 177 ff.), and a number of methods were developed for effecting isomerizations (see Windaus, Dithmar, Murke and Suckfüll, *loc. cit.*). With the recognition that irradiation results in the opening of one of the original rings, this line of attack was abandoned.

7-Dehydrocholesterol (p. 180). In an extensive study of the reactions of 7-dehydrocholesterol, Fr. Schenck, Buchholz and Wiese, *Ber.*, **69,** **2696** (1936), found the behavior of the substance practically identical with that of ergosterol. 7-Dehydrocholesterol was converted through a "pinacol" to a substance (norsterol) analogous to neoergosterol; it was transformed into a peroxide, a maleic anhydride addition product, isomeric cholesterols, and into a series of isomers, using the standard methods developed for ergosterol. Fr. Schenck, *Z. physiol. Chem.*, **243,** 119 (1936), investigating the preparative method, isolated a by-product in the conversion of cholesteryl acetate into 7-ketocholesteryl acetate (I) and identified the substance as 3,5-diacetoxycholestanone-6.

Quantitative Microhydrogenation (p. 183). Improved forms of apparatus are described by Jackson and R. N. Jones, *J. Chem. Soc.*, 895 (1936), Zechmeister and v. Cholnoky, *Chem. Ztg.*, **60,** 655 (1936), and Mayeda, *J. Pharm. Soc. Japan,* **56,** 511 (1936).

Dihydrovitamin D_2 (p. 184). The dihydro derivative resulting from the reduction of vitamin D_2 with sodium and propyl alcohol has been found by v. Reichel and Deppe, *Z. physiol. Chem.*, **239,** 143 (1936), to yield a crystalline trioxide on reaction with perbenzoic acid. A study of the further oxidation of the substance with chromic anhydride furnished evidence that one oxidic linkage is located at C_{22}-C_{23} and another at C_5-C_{10}. This accounts for all but one of the double bonds of dihydrovitamin D_2, and since the substance does not add maleic anhydride and exhibits no selective absorption in the ultraviolet region the third ethylenic linkage evidently does not occupy a position of conjugation and probably is at C_7-C_8, corresponding to one of the original centers of unsaturation in vitamin D_2 (formula VI, p. 185). It appears, therefore, that the reduction with sodium and alcohol consists in the addition of hydrogen at C_6 and C_{18}, that is, at the ends of a 1,4-conjugated system.

Lumisterol (p. 184). Although the evidence is not entirely complete, there are strong indications that lumisterol differs from ergosterol not in the positions of the double bonds or in the spatial arrangement of the hydroxyl group at C_3 but in the configuration at the asymmetric center C_{10} carrying the angular methyl group. That the nuclear ethylenic linkages are conjugated is shown perhaps most clearly by the observation of Heilbron, Spring and Stewart[31] that an additional double bond can be introduced by the action of mercuric acetate. It has been shown, moreover, by Dimroth, *Ber.*, **69,** 1123 (1936), that the resulting dehydrolumisterol has the same characteristic absorption spectrum, indicative of three conjugated double bonds, as dehydroergosterol (p. 175). If lumisterol contains a conjugated system, the character of the triol obtained by Heilbron, Spring and Stewart, and of a stereoisomeric triol studied by Dimroth, locates this system as extending from C_5 to C_8, exactly as in the case of ergosterol. The fact that lumisterol fails to form an insoluble digitonide would suggest (as stated on page 186) that this photoisomeride differs from ergosterol only in an epimeric arrangement of the hydroxyl group. If this were the case both sterols should yield the same unsaturated hydrocarbon on dehydration, but Heilbron, Spring and Stewart found that they yield different products.

For these reasons, Dimroth considers that lumisterol must have the same structure and the same configuration at C_3 as ergosterol. The change produced on irradiation must consist in a steric inversion at some center other than C_3, and most probably at a position coming under the activating influence of the light-absorbing conjugated system. Carbon atoms 9 and 10 are the most likely centers, since they are adjacent to double bonds, and since they are known to be involved in the ultimate rupture of the tetracyclic system. A further inference can be drawn from the consideration that on the basis of the evidence available dehydrolumisterol very probably has the same structure as dehydroergosterol (see formula, p. 175). Since in these compounds there is no longer a center of asymmetry at C_9, they must differ only in the configuration at C_{10}. It is inferred that lumisterol differs from ergosterol in this same respect.

Further observations of Dimroth lend weight to this view. Dehydroergosterol, he found, yields a perhydro derivative different from lumistanol, the hydrogenation product of lumisterol. Since carbon atom 10 retains its asymmetry throughout the changes involved, while the center C_9 becomes unsaturated in the former process and hence available for steric inversion in the hydrogenation, lumistanol and perhydrodehydrolumisterol can differ only in the configuration at C_9. Since neither substance is identical with ergostanol, they must differ from this compound in the configuration at the alternate center C_{10}, in conformity with the conclusion reached above.

Dimroth also made the striking discovery that perhydrodehydrolumisterol is identical with the perhydro derivative of pyrocalciferol. It is significant that the re-formation of the tetracyclic system involves the closing of a ring between the carbon atoms (9 and 10) assumed above to be involved in the first stage of the process of photoisomerism. Ring closure could result in configurations at C_9 and C_{10} different from the original ones. It appears from Dimroth's observation that the arrangement of the methyl group of pyrocalciferol is the same as in lumisterol, and it also is evident that no steric inversions occur in other parts of the molecule in the transformation of lumisterol through tachysterol to Vitamin D_2.

It is now evident that the assumption of an epimeric arrangement of the hydroxyl group of lumisterol and of the other isomerides of the series, based on the failure of these substances to give insoluble digitonides, is incorrect. Dimroth considers that the compounds all have the normal arrangement at C_3 of ergosterol and that the inability to combine with digitonin may be due to the abnormal spatial arrangement of the methyl group at C_{10}.

Vitamin D_2 or Calciferol (p. 185). Heilbron, R. N. Jones, Samant and Spring, *J. Chem. Soc.*, 905 (1936), confirmed the structure VIII for the aldehydic oxidation product by further analyses and by the observation that the absorption spectrum of the semicarbazone is that of an α, β-unsaturated compound. They further investigated the ozonolysis of vitamin D_2 (calciferol) and isolated as one product a keto acid ($C_{13}H_{20}O_3$) which must result from the fission of the molecule at the C_7-C_8 and the C_{22}-C_{23} ethylenic linkages. This can only be represented by a formula similar to X but having the side chain —$CH(CH_3)CO_2H$. As a second product of ozonolysis, formaldehyde was isolated and characterized as the dimedon derivative (the condensation product with two molecules of dimethyldihydroresorcinol). This establishes the presence of an exocyclic methylene group, as postulated by Windaus and Thiele[39] (formula VI), and removes any uncertainty in the evidence adduced by these investigators arising from the possibility of a rearrangement in the course of the Diels-Alder condensation or during the drastic pyrogenic reaction. The observations of the English investigators were further confirmed and extended by Windaus and W. Grundmann, *Ann.*, **524, 295** (1936), who isolated as oxidation products of vitamin D_2 the aldehyde $C_{21}H_{34}O$, the keto acid $C_{13}H_{20}O_3$, and an unsaturated ketone ($C_{19}H_{32}O$) which on hydrogenation yielded the ketone X (p. 185) of Windaus and Thiele. Windaus and Grundmann also obtained 20% of the theoretical amount of formic acid in the permanganate oxidation of vitamin D_2, and about 30% of the calculated amount of formaldehyde was obtained using ozone. Since ergosterol under similar conditions gives a few per cent of formic acid and a trace of formaldehyde, even though it contains no methylene group, Windaus regards the isolation of the other oxidation products as providing the most secure indication of the structure.

With the body of evidence now available the structure of the active irradiation product of ergosterol is clearly established in all details. In the light of Dimroth's work on lumisterol (p. 375), the formula for vitamin D_2 reproduced on pages 184 and 185 should be revised to indicate that the substance has the normal configuration at C_3 and is not an *epi*-compound.

Vitamin D (p. 186). Since the publication of the first edition the nature of the antirachitic principle of fish liver oils finally has been established beyond question as the result of further chemical and biological investigations of the problem. At the time of the previous review vitamin D_2 (calciferol), the active product of the irradiation of ergosterol, had been well characterized as to. structure, and it was recognized that the substance probably is not identical with natural vitamin D but is a good substitute for it. Active substances differing from vitamin D_2 only in relatively minor features of structure had been obtained also by the irradiation of 22-dihydroergosterol and of 7-dehydrocholesterol. Since these substances, of at least qualitatively similar biological actions, resemble one another closely in their structures and absorption spectra, it seemed likely that the antirachitic agent found in natural sources also is of the same general type. On the other hand, the optical properties noted for purified vitamin D concentrates seemed to indicate a striking disparity between the natural vitamin and the antirachitically active substances prepared from sterols (p. 179).

Attempts to identify natural vitamin D by comparing the biological actions of fish liver oils with those of known irradiation products were undertaken at an early date and, thanks to the efficacy of a special method of comparison, considerable progress was made. The method depends upon the fact that two substances of qualitatively similar physiological actions may differ appreciably in their relative potency when administered to different types of animals. Massengale and Nussmeier, *J. Biol. Chem.*, **87**, 423 (1930), were the first to compare vitamin D from cod liver oil with irradiated ergosterol by this method, and they found that, on the same rat-unit basis, irradiated ergosterol has less antirachitic effect than cod liver oil when tested on chicks. The conclusion that vitamin D and D_2 are not identical was confirmed by Steenbock, Kletzien and Halpin, *ibid.*, **97**, 249 (1932), and by others. Similarly, Waddell, *ibid.*, **105**, 711 (1934), observed that irradiated crude cholesterol is more effective in preventing rickets in chicks than an equivalent number of rat units of irradiated ergosterol [see also Dols, *Z. Vitaminforsch.*, **5**, 161 (1936)]. F. C. Koch, E. M. Koch and Ragins, *J. Biol. Chem.*, **85**, 141 (1929), found that cholesterol which has been purified through the dibromide shows increased activatability after it has been heated at 200° with traces of oxygen, and on comparing the rat and chick units Hathaway and Lobb, *ibid.*, **113**, 105 (1936), and Haman and Steenbock, *ibid.*, **114**, 505 (1936), found that irradiated heat-treated cholesterol contains a vitamin resembling that of liver oils more closely than irradiated ergosterol does. [Studies of the chemical activation of cholesterol are reviewed by Yoder, *ibid.*, **116**, 71 (1936). This line of work was initiated by the observation of Bills, *ibid.*, **67**, 753 (1926), that a weak antirachitic activation can be accomplished by treatment of cholesterol with the fuller's earth, floridin.]

The biological studies had reached a point where it appeared profitable to reinvestigate the provitamin of crude cholesterol, to attempt the isolation of the provitamin of heat-treated cholesterol, and to compare vitamin D concentrates with the irradiation product of 7-dehydrocholesterol by differential bio-assay, but at this phase in the work the problem was solved in investigations of a chemical nature conducted at the Göttingen laboratory.

The difficult task of isolating the antirachitic principle of tunny liver oil in a pure form was accomplished by Brockmann, *Z. physiol. Chem.*, **241**, 104 (1936). It seemed reasonable to suppose that the natural vitamin would bear a fairly close resemblance to vitamin D_2 in structure, even though it might not be identical with this substance; and Brockmann, assuming that there would be a fair correspondence in the solubilities, adsorbabilities, absorption spectra, and other properties of the two substances, designed a procedure for the isolation of vitamin D based upon a number of trial experiments with vitamin D_2. The preliminary work included the development of a colorimetric method for the quantitative determination of vitamin D_2 (or D) based upon the measurement of the intensity of a characteristic absorption band at 500 mμ of an antimony trichloride complex. [Brockmann and Y. H. Chen, *ibid.*, **241,** 129 (1936). For comments concerning the use and history of this colorimetric method, see F. A. Robinson and F. E. Young, *Chemistry and Industry,* **55,** 835 (1936). For a colorimetric determination employing aluminum chloride, see Tzoni, *Biochem. Z.*, **287,** 429 (1936)]. Since the complex from vitamin A has an absorption maximum at 620 mμ the presence of this substance does not interfere with the determination. Tachysterol is the only related substance giving the specific test.

A liver oil concentrate containing by assay 0.32% of vitamin D was used as the starting material, and on distribution between 90% methanol and ligroin the bulk of the vitamin A was retained in the former solvent while the vitamin D collected in the ligroin. Extraction of the ligroin solution with 95% methanol removed the vitamin D, and much inactive material was retained in the ligroin. A further enrichment was accomplished by chromatographic adsorption on aluminum hydroxide, a dye of the same degree of adsorbability as vitamin D_2 being used as an indicator to reveal the adsorption zone. Finally the dye was removed with alkali, cholesterol was precipitated as the digitonide, and the active principle was esterified with 3,5-dinitrobenzoyl chloride. After purification by adsorption, a crystalline, 3,5-dinitrobenzoate, m.p. 128-129°, was isolated. Hydrolysis gave a non-crystalline sterol having an ultraviolet absorption spectrum similar to that of vitamin D_2 (maximum at 265 mμ and an antirachitic activity of the same order of magnitude. The crystalline ester was not identical with that of the active irradiation product of ergosterol and, indeed, it differed from this substance in composition. The composition, however, was that of the 3,5-dinitrobenzoate of an antirachitic substance known as vitamin D_3, which Windaus, Fr. Schenck and v. Werder, *Z. physiol. Chem.*, **241,** 100 (1936), had just prepared by the irradiation of 7-dehydrocholesterol (p. 180). The two esters melted at the same temperature and direct comparison established their complete identity. Grab, *ibid.*, **243,** 63 (1936), later compared the antirachitic activity of Brockmann's product with that of vitamin D_3, using both rats and chicks, and found that the effective dosages agreed so closely that the identity of the biological activities cannot be questioned. He also established a quantitative correspondence in the biological actions of tunny liver oil and crystalline vitamin D_3 and thus provided independent evidence of the identity of the natural vitamin.

The isolation of the natural vitamin and its prompt identification by comparison with a substance which already had been produced by chemical means, has finally solved a most important and perplexing problem. The natural substance, or vitamin D_3 from 7-dehydrocholesterol, can be assigned with assurance a structure similar to that of vitamin D_2 (formula VI, p. 185) but having the saturated side chain of cholesterol ($-C_8H_{17}$). The mother substance of the vitamin very probably is cholesterol, but the manner in which the transformation occurs is not yet clear. It seems hardly possible that the vitamin arises from the irradiation of a provitamin in the fish, but only physiological investigation can determine whether the final vitamin is acquired from irradiated food, or by a synthesis requiring no radiant energy in the organism of the fish. From a comparison of the absorption spectra, E. M. Koch and F. C. Koch, *J. Biol. Chem.*, **116,** 757 (1936), concluded that the activatable contaminant of crude spinal cord cholesterol probably is 7-dehydrocholesterol, but that the provitamin D of heated, purified cholesterol is a distinctly different substance.

From the work of Brockmann it is clear that the early reports of the properties of natural vitamin D (Ender, Rygh, pp. 178, 179) are erroneous. The substance is optically active, it has an absorption spectrum characteristic of sterols with three conjugated double bonds, and it readily adds maleic anhydride. According to a preliminary report of Haslewood and Drummond, *Chemistry and Industry,* **55,** 598 (1936), still other substances of antirachitic activity may be present in fish liver oils. Brockmann's observations, however, have been confirmed by Simons and Zucker, *J. Am. Chem. Soc.*, **58,** 2655 (1936), who isolated from tunny liver oil, by a process not involving chromatographic technique, a substance whose 3,5-dinitrobenzoate melted at 128.5° and which differed only slightly from Brockmann's compound in biological activity and in the character of the absorption band. Neracher and Reichstein, *Helv. Chim. Acta,* **19,** 1382 (1936), obtained from the same source three crystalline dinitrobenzoates, but the alcohols proved to be inactive. Searching for the provitamin present in about 0.18% in crude cholesterol from egg yolk, Windaus and Stange, *Z. physiol. Chem.*, **244,** 218 (1936), isolated ergosterol. They consider it probable that this sterol is resorbed in small amounts from the diet and does not arise in the organism of the hen.

Relationship Between Structure and Antirachitic Activity. It is now known that irradiated 22-dihydroergosterol (contrary to the preliminary reports, p. 180), is more potent than vitamin D_2 and nearly as active as vitamin D_3 [Grab, *loc. cit.*; McDonald, *J. Biol. Chem.*, **114,** Proc.

LXV (1936)]. The extra methyl group in the side chain appears to have but little influence in determining the physiological potency. According to Grab's results, vitamin D_2 is somewhat less potent than vitamin D_3, indicating that the double bond of the side chain detracts from the activity. The most essential feature of structure doubtless is the presence of a system of three conjugated double bonds extending between the original rings A and C, and in order for a sterol to function as a provitamin it evidently must contain a diene system between positions 5 and 8. In extension of these observations, additional sterols of the type defined have been investigated at the Göttingen laboratory. 7-Dehydrositosterol [Wunderlich, *Z. physiol. Chem.*, **241**, 116 (1936)] gave on irradiation a substance of high antirachitic activity, but, surprisingly enough, the irradiation product obtained from 7-dehydrostigmasterol [Linsert, *ibid.*, **241**, 125 (1936)] proved to be inactive, or at the most very feebly active. Bann, Heilbron and Spring, *J. Chem. Soc.*, 1274 (1936), attempted to prepare a similarly unsaturated sterol by a different method but encountered an unexpected obstacle. Treatment of 7-ketocholesteryl acetate (formula I, p. 180) with three equivalents of methylmagnesium iodide gave 7-hydroxy-7-methylcholesterol, but on dehydration of this carbinol (as the benzoate) an ethylenic linkage was introduced not at the desired 7,8-position, but in the alternate exocyclic position. Irradiated 7-methylenecholesterol, as anticipated, is antirachitically inactive. In another investigation Barr, Heilbron, Parry and Spring, *ibid.*, 1437 (1936) discovered a new route to 7-dehydrocholesterol. Noting that cholesterol is remarkably stable to neutral potassium permanganate, these workers tried oxidizing cholesteryl hydrogen phthalate with alkaline permanganate. Of three oxidation products isolated, one proved to be the acid phthalate of a 7-hydroxycholesterol, m.p. 184-185°, for the diol formed a dibenzoate which yielded 7-dehydrocholesteryl benzoate on pyrolysis. The new diol is a stereoisomer of the 7-hydroxycholesterol of Windaus, Lettré and Schenck,[24] the difference being in the configuration at C_7. To distinguish the isomers, the diol of Windaus, Lettré and Schenck is appropriately named 7(α)-hydroxycholesterol, while that of the English investigators is the 7(β)-hydroxy derivative.

Other Studies (addition to p. 186). Vanghelovici and Vasiliu, *Bul. Soc. Chim. România*, **17**, 249 (1935), prepared 6-aminocholestane and investigated other nitrogen-containing sterol derivatives. It was observed that ergosterol is converted by the action of phosphorus trichloride into an ergostatetraene ($C_{28}H_{42}$), m.p. 102°. This forms a hydrogen chloride addition product, m.p. 107°. Further studies of nitrogen-containing bile acid derivatives are reported by M. Schenck, *Z. physiol. Chem.*, **239**, 135 (1936); **242**, 81, **244**, **245** (1936). Lettré and Hagedorn, *ibid.*, **242**, 210 (1936), investigated synthetic glycosides of sterols in the hope of defining the features of structure responsible for the hemolytic action of the neutral saponins of the digitalis group (p. 322), but substances of a high degree of water-solubility have not yet been obtained. Dane and Brady, *ibid.*, **244,** 241 (1936), prepared the 3-glucoside of desoxycholic acid with the view of increasing of the digitalis-like action of this bile acid.

Chapter V

Combined Form of Oestriol (p. 194). S. L. Cohen and Marrian, *Biochem. J.*, **30,** 57 (1936), isolated from human pregnancy urine a water-soluble, ether-insoluble substance having the properties and approximately the composition of an oestriol glucuronic acid ($C_{24}H_{32}O_9$). S. L. Cohen, Marrian and Odell, *ibid.*, **30,** 2250 (1936), later isolated the pure crystalline sodium salt of oestriolglucuronide and showed that the glucuronic acid is joined to the oestriol by a glucosidic link to one of the two secondary hydroxyl groups, the phenolic hydroxyl being free. The oestriol in the glucuronide has only about 1/17 the potency of the same amount of uncombined oestriol.

Colorimetric Determinations (pp. 194-195). Schmulovitz and Wylie, *J. Lab. Clin. Med.*, **21,** 210 (1935); *J. Biol. Chem.*, **116,** 415 (1936), used the orange or red colors of the azo dyes, formed by coupling oestrone and oestriol with diazotized *p*-nitroaniline or sulfanilic acid, as a means of estimating these substances in extracts of human pregnancy urine. Chevallier, Cornil and Verdollin, *Bull. acad. méd.*, **114,** 171 (1935), used the characteristic ultraviolet absorption band at 280 mμ to detect oestrogenic substances in urinary extracts. Pincus, Wheeler, G. Young and Zahl, *J. Biol. Chem.*, **116,** 253 (1936), compared several of the previous colorimetric methods of estimation and developed a new test based upon a color reaction with benzoyl chloride. A more intense color is obtained with oestrone than with oestriol, and the test distinguishes these substances from oestradiol (p. 213), which does not give the typical color.

Derivatives of Oestrone (p. 195). Dirscherl, *Z. physiol. Chem.*, **239,** 49 (1936), prepared the ethyl carbonic ester of oestrone ($ROCO_2C_2H_5$), m.p. 115°, corr., by the action of ethyl chloroformate and pyridine on the hormone or by interaction with phosgene and pyridine, followed by alcoholysis of the chloroformyl ester (ROCOCl). The chloroformyl ester, m.p. 101-102°, was found to have an enhanced oestrogenic activity.

δ-Follicular Hormone (p. 195). The substance described by Schwenk and Hildebrandt[26] was later separated from the urine of mares by Wintersteiner, Schwenk and co-workers and found to be a mixture from which one component was isolated in a pure form through the picrate [Wintersteiner, Schwenk and Whitman, *Proc. Soc. Exptl. Biol. Med.*, **32,** 1087 (1935); Wintersteiner, Schwenk, Hirschmann and Whitman, *J. Am. Chem. Soc.*, **58,** 2652 (1936)]. The new compound, m.p. 215-217°, has the composition $C_{18}H_{20}O_2$ and was characterized as a diol having the structure of a dihydro derivative of equilenin (p. 202). The phenolic monobenzoate on oxidation gave a ketone identical with equilenin benzoate. The dihydroequilenin from urine possesses only about one-half the oestrogenic potency of equilenin (the potent, oily diol of David, p. 215, may have contained stereoisomers).

Standardization of the Sex Hormones (p. 196). At the second conference held under the auspices of the League of Nations, a second international unit, the "benzoate unit," was defined as the specific activity of 0.1 γ of a standard preparation of the pure monobenzoate of oestradiol, (p. 214) m.p. 194-195° [*Z. angew. Chem.*, **48,** 805 (1935)]. The international unit for the male hormones is defined in terms of the activity of 0.1 mg. of a pure androsterone preparation measured in the comb growth test. For the corpus luteum hormones the unit of activity is that of 1 mg. of β-progesterone (Corner-Allen or Clauberg test).

Extraction of Oestrone (p. 197). A number of improvements in the process of Beall and Marrian[34] are described by Beall and Edson, *Biochem, J.*, **30,** 577 (1936).

Reagents for the Isolation of Ketones (p. 197). A convenient procedure for the preparation of the Girard reagent in 90% yield starting with ethylchloroacetate, trimethylamine, and hydrazine hydrate is described by Girard and Sandulesco, *Helv. Chim. Acta,* **19,** 1095 (1936). The reagent, trimethylaminoacetohydrazide hydrochloride (betaine-hydrazide hydrochloride) must be stored with some care as it is hygroscopic and undergoes decomposition in a moist atmosphere. The condensation is best carried out in alcoholic solution containing 10% acetic acid, refluxing for one-half hour usually being sufficient. The condensation products from ketones are hydrolyzed very easily by mineral acids, while those from aldehydes are so stable to acid hydrolysis that a separation of ketones from aldehydes can be made without difficulty. No practical process was found for the regeneration of aldehydes. Diaryl ketones react only very slowly with the reagent. Girard and Sandulesco developed a new test for ketones based upon the formation of a colored precipitate on adding mercuric and potassium iodides to an aqueous solution of the condensation product; and it is reported that the presence of a few γ of oestrone can be recognized easily by this method in a micro test. These investigators describe a second reagent which differs from the first only in the replacement of the trimethylamine residue by pyridine, and as it is not hygroscopic the substance is recommended for technical isolations. It is not suitable for use in the qualitative precipitation test.

Anchel and Schoenheimer, *J. Biol. Chem.*, **114,** 539 (1936), found the Girard reagent somewhat unsatisfactory for the isolation of cholestanone because the condensation product is hydrolyzed with such great ease as to make separations difficult. [See, however, Reichstein, *Helv. Chim. Acta,* **19,** 1107 (1936)]. They investigated reagents whose condensation products form water-soluble alkali salts, and found two compounds which offer certain distinct advantages, particularly when used in combination with one another. One of these, carboxymethoxylamine ($H_2NOCH_2CO_2H$), is easily prepared from the sodium derivative of acetoxime and ethyl chloroacetate [Borek and Clarke, *J. Am. Chem. Soc.*, **58,** 2020 (1936)]. It reacts rapidly with sterol ketones in alcoholic solution, and the products of the type $R_2C{=}NOCH_2CO_2H$ can be extracted from mixtures by distribution between potassium carbonate solution and ether, the product separating as a precipitate when the aqueous layer is acidified. The oxime acids are not attacked by air, and this is a convenient form in which to isolate the total ketones from unsaponifiable material. After regeneration of the total ketones, a separation of the α, β-unsaturated ketone cholestenone from cholestanone and coprostanone can be effected with the use of a second reagent, *p*-carboxyphenylhydrazine ($H_2NNHC_6H_4CO_2H$). While the hydrazones of the saturated ketones are easily cleaved on refluxing the mixture with alcoholic formaldehyde solution, the hydrazone of cholestenone is not attacked under these conditions. This ketone can be recovered by refluxing in an alcoholic solution of pyruvic acid. *p*-Carboxyphenylhydrazine is not used in the first, gross extraction because the phenylhydrazones are autoxidizable, making it necessary to work as far as possible in the absence of air.

Influence of Oestrin on Plant Growth (pp. 199-200). In further investigations the results have been almost entirely negative. [Harder and Störmer, *Nachr. Ges. Wiss., Göttingen,* 11 (1934); Störmer, *Biochem. Z.*, **285,** 29 (1936); Teodoro and Zampetti, *Arch. ist. biochim. ital.*, **7,** 423 (1935); Tincker, *Ann. Appl. Biol.*, **22,** 619 (1935); Chouard, *Compt. rend. soc. biol.*, **122,** 823 (1936)]. Positive results are reported by Scharrer and Schropp, *Biochem. Z.*, **281,** 314 (1935).

X-Ray Analysis (p. 206). X-ray crystallographic data for oestrone and other hormones are given by Bernal and Crowfoot, *Z. Krist.*, **93,** 464 (1936).

Hydrogenation of Oestrone (p. 213). On hydrogenating the hormone or its acyl derivatives in the presence of Adams' catalyst in neutral or alkaline alcoholic solution, Dirscherl, *Z. physiol. Chem.*, **239,** 53

(1936), obtained oestradiol (m.p. 174-175°) as the sole product. On conducting the reaction at room temperature in acetic acid solution or in alcohol containing hydrochloric acid, he found that the aromatic nucleus is attacked, usually even before the carbonyl group, giving mixtures of ketonic hexahydro derivatives, octahydro derivatives, and hexahydrodesoxyoestrones. An oestranediol-3,17, m.p. 210-211°, was isolated in a pure condition from the mixture of isomeric octahydro compounds, and a ketonic hexahydro derivative was isolated as the semicarbazone.

Isolation of Oestradiol (p. 214). Details of the isolation of the hormone are reported by MacCorquodale, Thayer and Doisy, *J. Biol. Chem.*, **115**, 435 (1936). In the most satisfactory procedure oestradiol was isolated not as the (mono) *m*-bromobenzoate, prepared by the Schotten-Baumann reaction, but as the di-*α*-naphthoate, the slight solubility of which in ethyl alcohol permits a ready separation from contaminating substances. The preparation of the derivative was carried out in pyridine solution and the excess *α*-naphthoyl chloride was removed by adding excess glycine and subsequently extracting the resulting *α*-naphthoylglycine with sodium bicarbonate solution. The free hormone recovered after hydrolysis (m.p. 171-172°) was identical in melting-point characteristics and in bio-assay with a sample of oestradiol (m.p. 172-173°) prepared in quantitative yield by the hydrogenation of oestrone in the presence of Adams' catalyst. The complete recovery as oestradiol of all the oestrogenic material of the four tons of sow ovaries processed in the course of the work would have given only 25 mg. of the hormone, and the isolated material amounted to about one-half of this quantity.

Not long after the discovery of the hormone by Doisy and co-workers, Wintersteiner, Schwenk and Whitman, *Proc. Soc. Exptl. Biol. Med.*, **32**, 1087 (1935), reported isolating oestradiol from the pregnancy urine of mares.

Supposed Activity of Degradation Products (p. 215). The early report that certain oxidation products of oestriol methyl ether are more active than oestrone has been retracted. MacCorquodale, Levin and Thayer, *J. Biol. Chem.*, **105**, lv (1934), state that none of the degradation products of oestrone and oestriol investigated has any significant oestrogenic activity.

Oestrogenic Activity of Synthetic Compounds (pp. 215-217). A further investigation of 9,10-dialkyl-9,10-dihydroxy-9,10-dihydro-1,2,5,6-dibenzanthracenes (III, p. 216) and related diols has been made by Cook, Dodds and Lawson, *Proc. Roy. Soc.*, (London), **B121, 133** (1936). Seven new dialkyl derivatives of the type III were examined for oestrogenic activity, but the potency in no case equaled that of the di-*n*-propyl diol, the most active of the substances previously described. Branching of the side chains results in a marked decrease in the activity, the di-*i*-propyl compound being only one-tenth as active as the di-*n*-propyl diol. The introduction of double bonds produces an even more pronounced change in the biological actions of the molecule, for the di-allyl compound gave entirely negative results when injected into ovariectomized rats in 10 mg. doses. An interesting test was made of the effect of cyclization of the aliphatic chain. While the di-*n*-amyl compound is inactive in large doses, the dicyclopentyl compound gave positive results in 0.5 mg. doses. The English investigators note that the configurations of the diols have not been determined and that it is not yet known if the substances studied are cis or trans compounds, or mixtures. Differences in the stereoisomeric type or in the composition of mixtures might seriously obscure the correlation of structure with biological activity. Whether the synthetic diols are single individuals or mixtures, they reproduce all the known biological actions of naturally occurring oestrone. The substances produce vaginal changes in rats and mice, they stimulate uterine enlargement and induce premature puberty in immature animals, they produce plumage changes in capons (p. 216), and reproduce pathological changes resulting from the administration of oestrone [p. 218. Burrows, Ref. 99, *British Journal of Surgery,* **23,** 658 (1935)]. Cook, Dodds and Lawson also found that the di-*n*-propyl diol, like oestrone, can prepare the uterus for the endometrial proliferation brought about by progesterone (pp. 241-242), and Wolfe, *Am. J. Physiol.,* **115,** 665 (1936), observed that administration of the diol to castrated female rats prevents the appearance of castration cells in the anterior lobe of the pituitary.

Other dialkyl diols of analogous structure were prepared by the addition of Grignard reagents to anthraquinone, phenanthrenequinone, chrysenequinone, 1,2-benzanthraquinone, and the *Bz*-tetrahydro derivatives of 1,2- and 2,3-benzanthraquinone. Oestrogenic activity of a low order was shown by the diphenyl diols from chrysenequinone and 1,2-benzanthracene, while all other members of these series were inactive. In the course of the work 1-hydroxy-1,2,3,4-tetrahydrophenanthrene was found inactive in rats in doses of 100 mg.

While all of the previously described oestrogenic agents except the weakly acting 1-ketooctahydroanthracene IV (p. 217) contain the phenanthrene ring system, Dodds and Lawson, *Nature,* **137,** 996 (1936), discovered that a number of substances not related to phenanthrene exhibit definite oestrogenic activity [see also Dodds, *Helv. Chim Acta,* **19,** E49 (1936)]. 7,8-Dihydroxy-7,8-di-(α-naphthyl)-acenaphthene, administered in 100 mg. doses, will maintain a rat in full oestrus for a prolonged period, and it is active in doses as small as 10 mg. A number of other dihydroxy compounds were found to possess definite oestrogenic activity when injected in rats in 100 mg. dosage, the list including such comparitively simple compounds as 4,4′-dihydroxydiphenyl, 4,4′-dihydroxydiphenylmethane, and di-(α-naphthyl)-carbinol. The effective dosages of these compounds, as far as determined, are several hundred times larger than for the dialkyl diols of the dibenzanthracene series, but the results illustrate further the absence of a high degree of structural specificity in this type of female hormonal activity.

Pincus and Werthessen, *Science*, **84**, 45 (1936), developed a special method of assay dependent upon the intraperitoneal, rather than subcutaneous, injection of the substance tested. While the results have not been correlated with those obtained by the standard Allen-Doisy technique, the method appears to offer a preliminary guide in the study of synthetic substances. Of a number of phenanthrene and hydrophenanthrene derivatives tested, the most active was 6,7-dihydroxy-1,2,3,4,9,10, 11,12-octahydrophenanthrene-11,12-dicarboxylic anhydride [Fieser and Hershberg, *J. Am. Chem. Soc.*, **58**, 2314 (1936)], which was rated as more potent than 1-keto-1,2,3,4-tetrahydrophenanthrene.

Oestrone from Ergosterol (p. 219). The conversion of dehydroneoergosterol into oestrone has been realized by Marker, O. Kamm, Oakwood and Laucius, *J. Am. Chem. Soc.*, **58**, 1503 (1936); paper XI in press. It was found that on reduction with sodium and amyl alcohol dehydroneoergosterol is attacked largely at ring B, giving a phenolic tetrahydro derivative. Applying Ruzicka's method for the elimination of the sterol side chain (p. 227), this compound was oxidized in the form of the acetate and yielded, after hydrolysis, a substance identical with natural oestrone. The yields realized in these operations are not reported. By improved procedures, ergosterol was converted through ergopinacol and neoergosterol into the required dehydroneoergosterol with an overall yield of about 4% by weight. Whether or not the method proves of practical importance for the preparation of oestrone, the observation is of considerable significance in providing a clear proof that the configuration at the asymmetric centers C_{13} and C_{14} is the same in oestrone as in ergosterol and therefore in cholesterol. The certain evidence that oestrone contains an angular methyl group at C_{13} and a carbonyl group at C_{17} (pp. 211-212) now affords a rigid proof of the location of the corresponding methyl group and of the side chain in the sterols.

Bardhan's Synthesis (p. 220). In another preliminary announcement Bardhan, *Chemistry and Industry*, **55**, 879 (1936), has reported a further variation of the scheme of synthesis illustrated in formulas I-III. Phenylethyl bromide was condensed with ethyl α-acetyl-β-ketopimalate to give ethyl α-(β′-phenylethyl)-β-ketopimalate. This was cyclized with sulfuric acid to a Δ^1-dihydronaphthalene derivative. The third ring was closed by an ester condensation with sodium, and 1-keto-1,2,3,4,9,10-hexahydrophenanthrene was obtained on hydrolysis. Details of the preparation of 3′-keto-3,4-dihydro-1,2-cyclopentenophenanthrene (III) are reported by Bardhan, *J. Chem. Soc.*, 1848 (1936).

Derivatives of Phenanthrene-1,2-dicarboxylic Anhydride (p. 221). By application of the standard synthesis (see VIII ——→ IX) to suitably substituted naphthalene derivatives, A. Cohen, Cook and Hewett, *J. Chem. Soc.*, 52 (1936), prepared 7-methoxyphenanthrene-1,2-dicarboxylic anhydride, and Fieser and Hershberg, *J. Am. Chem. Soc.*, **58,** 2314, 2382 (1936) prepared the 9-methoxy and the 5,9-dimethoxy derivatives of the anhydride. Starting with the ester of phenanthrene-1,2-dicarboxylic acid, L. F. Fieser, M. Fieser and Hershburg, *ibid.*, **58,** 2322 (1936), prepared 1′,3′-diketo-1,2-cyclopentenophenanthrene by condensation with ethyl acetate and saponification of the diketo ester. The 5,9-dimethoxyphenanthrindanedione was prepared in a similar manner [*ibid.*, **58,** 2382 (1936)]. A. Cohen, *Nature*, 136, 869 (1935), prepared phenanthrene-1,2-dicarboxylic anhydride and its 7-methoxy derivative by an interesting application of the Diels-Alder reaction. It was found that 1-vinylnaphthalene combines readily with maleic anhydride at ordinary temperature to give a tetrahydrophenanthrene-1,2-dicarboxylic anhydride. The fully aromatic compound was obtained by dehydrogenation with platinum black. A similar synthesis was achieved with 7-methoxy-1-vinylnaphthalene.

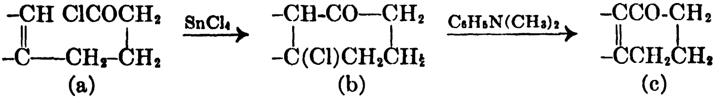
7-Methoxy-1-ketotetrahydrophenanthrene (p. 221). Two alternate methods have been described for the synthesis of the compound of Butenandt and Schramm[9] (ether of XI). A Cohen, Cook and Hewett, *J. Chem. Soc.*, 52 (1936), converted β-(6-methoxy-1-naphthyl)-ethyl alcohol (p. 210) into γ-(6-methoxy-1-naphthyl)-butyric acid by the malonic ester synthesis and cyclized the product with 80% sulfuric acid. Haberland, *Ber.*, **69,** 1380 (1936), prepared the same intermediate in still another manner. 6-Methoxy-1-tetralone was converted by the Reformatsky condensation with ethyl bromoacetate, followed by dehydration and reduction with sodium and alcohol, into β-(6-methoxy-1-tetralyl)-ethyl alcohol. The chain was lengthened by the malonic ester synthesis and γ-(6-methoxy-1-naphthyl)-butyric acid was obtained in excellent yield by dehydration with sulfur. Kon and F. C. J. Ruzicka, *J. Chem. Soc.*, 187 (1936), synthesized 8- and 9-hydroxy-1-ketotetrahydrophenanthrene starting with the β-methoxynapthylethyl alcohols obtained by the action of ethylene oxide on the Grignard reagents from 1-bromo-4-methoxynaphthalene and 1-bromo-5-methoxynaphthalene. The chains were lengthened by the malonic ester synthesis, the γ-arylbutyric acids were cyclized, and the ketones demethylated. By application of the standard methods the naphthylethyl alcohols were converted also into 8- and 9-methoxycyclopentenophenanthrene.

γ-*m*-Methoxyphenylbutyric Acid (p. 222). In preparing further quantities of the acid, R. Robinson and J. Walker, *J. Chem. Soc.*, **192,** 747 (1936), introduced certain technical variations in the synthesis (b) from *m*-methoxybenzaldehyde (condensation of the aldehyde with methyl acetate or with malonic acid in pyridine, introduction of an ester group by a Grignard reaction with methyl chloroformate). Another method of preparation was investigated by Chuang and Huang, *Ber.*, **69,** 1505 (1936), and by Martin, *J. Am. Chem. Soc.*, **58,** 1438 (1936). β-Benzoylpropionic acid was converted through the *m*-nitro derivative, the amine, and the hydroxy compound into Thompson's β-*m*-methoxybenzoyl propionic acid (XIII) and this was reduced by the Clemmensen method. The reactions proceed satisfactorily except in the last step. Martin found that considerable resinification occurs in the reduction of any but very small quantities, even when employing toluene (p. 347). No difficulty was encountered in the preparation of γ-3-methoxy-4-methylphenylbutyric acid by the same method.

Robinson-Rapson Synthesis (pp. 222-223). The structure XVI assigned to the condensation product has been confirmed by X-ray crystallographic analysis and by the observation that the compound on hydrogenation yields a tetrahydro derivative of alcoholic function, as shown by acetylation [Crowfoot, Rapson and R. Robinson, *J. Chem. Soc.*, 757 (1936)]. Further evidence that the condensation proceeds as indicated is furnished by the successful use of the method in the synthesis of known hydrocarbons. From α-tetralone and acetylcyclohexene, Peak and R. Robinson, *ibid.*, 759 (1936), obtained in excellent yield a mixture of three isomeric ketodecahydrochrysenes. Two of these are believed to be stereoisomers and the third is regarded as having the double bond in a different location. The nature of the ring system was established by conversion to chrysene. Hawthorne and R. Robinson, *ibid.*, 763 (1936), found that the condensation of α-tetralone with acetylcyclopentene proceeds less smoothly, and only one ketotetrahydrocyclopentanophenanthrene was isolated. Peak, R. Robinson and J. Walker, *ibid.*, 752 (1936), made a preliminary study of other possible variations of the Knoevenagel reaction for synthetic purposes. Rapson, *ibid.*, 1626 (1936), investigated the condensation of 2-carbethoxycyclohexanone and the corresponding cyclopentanone derivative with unsaturated methyl ketones.

Robinson-Schlittler Synthesis (p 223). As an alternate route to the intermediate diketone XIX, Hewett, *J. Chem. Soc.*, 50 (1936), investigated the condensation of β-*m*-methoxyphenylethyl bromide with the potassium derivative of dihydroresorcinol. Although some of the desired compound was obtained, the chief product was that of O-alkylation and the process was declared unsuitable for preparative purposes.

As a further step toward the hormone type of structure, R. Robinson and J. Walker, *ibid.*, 192 (1936), succeeded in preparing the 2-methyl derivative of 7-methoxy-1-ketohexahydrophenanthrene, XX. This was accomplished by employing ethyl α-acetyl-α′-methylglutarate in the first step of the synthesis. The cyclization of the methyl derivative of the diketone XIX might occur in two ways, but by varying the last two stages of the synthesis it was found that the ring closure involves the less hindered carbonyl group, as anticipated. The methylated keto ester corresponding to XVIII was cyclized with sulfuric acid at -15° to the 1-substituted Δ^1-dihydronaphthalene derivative. In order to close the third ring, use was made of an adaptation of the Darzens reaction [*Compt. rend.*, **150,** 707 (1910)] first used for the synthesis of cyclic compounds by Cook and Lawrence, *J. Chem. Soc.*, 1637 (1935). This consists in the intramolecular condensation of an unsaturated acid chloride (a) to a chloroketone (b),

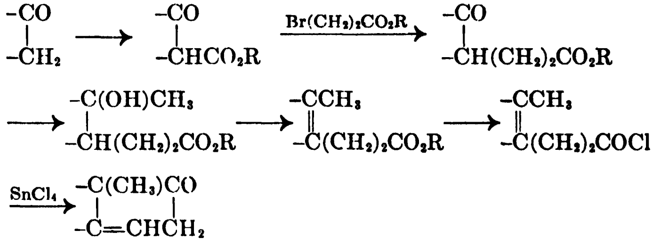


followed by the elimination of hydrogen chloride with dimethylaniline to give an unsaturated ketone (c). The final product obtained in this way was identical with the substance prepared by the first synthesis and consequently the location of the methyl group at the 2-position is established.

For the application of another plan of synthesis the saturated ketone corresponding to XX was required. Having no success in attempting to effect a direct saturation of the ethylenic linkage, R. Robinson and J. Walker, *ibid.*, 747 (1936), reduced XX to a saturated alcohol which was then oxidized to the ketone. The crystalline 7-methoxy-1-ketooctahydrophenanthrene isolated from the resulting mixture appeared from X-ray crystallographic analysis to have the trans configuration. When the oxidation was not conducted under very mild conditions, the hydronaphthalene nucleus was aromatized in the course of the reaction and the ketone of Butenandt and Schramm (ether of XI, p. 221) was obtained. Starting with the saturated trans ketone, a carbethoxy group was introduced at the 2-position by condensation with ethyl oxalate and decomposition of the oxalyl derivative, and a methyl group was then introduced at position 2 by alkylation of the β-keto ester.

Chuang's Syntheses (addition to p. 223). The Darzens reaction, introduced as a method of cyclization by Cook and Lawrence (see above), was employed by Chuang, Tien and Ma, *Ber.*, **69,** 1494 (1936), in the elaboration of two interesting general methods for the synthesis of polycyclic compounds containing angular methyl groups. The two schemes are indicated by means of partial formulas. Isomers can arise in the Darzens cyclization and only one possible location of the new double bond is shown.

(a)

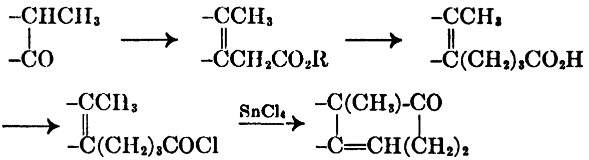


$$\begin{array}{l}-CO\\ \,|\\-CH_2\end{array}\longrightarrow\begin{array}{l}-CO\\ \,|\\-CHCO_2R\end{array}\xrightarrow{Br(CH_2)_2CO_2R}\begin{array}{l}-CO\\ \,|\\-CH(CH_2)_2CO_2R\end{array}$$

$$\longrightarrow\begin{array}{l}-C(OH)CH_3\\ \,|\\-CH(CH_2)_2CO_2R\end{array}\longrightarrow\begin{array}{l}-CCH_3\\ \,\|\\-C(CH_2)_2CO_2R\end{array}\longrightarrow\begin{array}{l}-CCH_3\\ \,\|\\-C(CH_2)_2COCl\end{array}$$

$$\xrightarrow{SnCl_4}\begin{array}{l}-C(CH_3)CO\\ \,|\qquad\quad |\\-C{=}CHCH_2\end{array}$$

(b)



$$\begin{array}{l}-CHCH_3\\ \,|\\-CO\end{array}\longrightarrow\begin{array}{l}-CCH_3\\ \,\|\\-CCH_2CO_2R\end{array}\longrightarrow\begin{array}{l}-CCH_3\\ \,\|\\-C(CH_2)_3CO_2H\end{array}$$

$$\longrightarrow\begin{array}{l}-CCH_3\\ \,\|\\-C(CH_2)_3COCl\end{array}\xrightarrow{SnCl_4}\begin{array}{l}-C(CH_3)\text{-}CO\\ \,|\qquad\qquad |\\-C{=}CH(CH_2)_2\end{array}$$

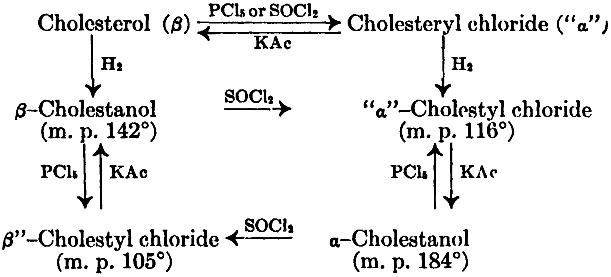
Chuang, Tien and Ma prepared angular methyl derivatives of α-hydrindanone and of α-octalone by methods (a) and (b), respectively. The 9-methyloctalin ($\Delta^{4,10}$ or $\Delta^{5,10}$) was not affected by treatment with selenium at 400°, but yielded naphthalene when the temperature was raised to 450°.

Natelson-Gottfried Synthesis (addition to p. 223). Natelson and Gottfried, *J. Am. Chem. Soc.*, **58,** 1432 (1936), explored an interesting plan of synthesis which involves the construction of a molecule having all features of the structure of 3′-keto-1,2-cyclopentenophenanthrene except the diphenyl linkage between rings A and C. This linkage might then be established by a suitable process of cyclization. Furthermore, by suitable modification of the tricyclic compound it might be possible to approach the type of structure found in vitamin D. Natelson and Gottfried developed an ingenious process for the synthesis of the desired 4-(β-phenylethyl)-hydrindone-1 and are investigating the above possibilities.

Male Hormone Activity of Hydrogenation Products of Oestrone (p. 226). In a further investigation of crystalline products of the nuclear hydrogenation of oestrone, (p. 384) and of mixtures, Dirscherl,

J. Kraus and H. E. Voss, *Z. physiol. Chem.*, 241, 1 (1936), came to the conclusion that crystalline preparations of oestrone from mare's and stallion's urine (but not those from human pregnancy urine) contain an unknown precursor which by hydrogenation is converted into a product with a powerful action on the seminal vesicles but inactive in the comb growth test.

Epimeric Cholestyl Chlorides (p. 230). The information available concerning the chloro compounds obtainable from cholesterol, dihydrocholesterol (β-cholestanol), and *epi*dihydrocholesterol (α-cholestanol) is summarized in the accompanying chart.


Cholesterol (β)
PCl_5 or $SOCl_2$
KAc
Cholesteryl chloride ("α")
H_2
H_2
β-Cholestanol (m. p. 142°)
$SOCl_2$
"α"-Cholestyl chloride (m. p. 116°)
PCl_5
KAc
PCl_5
KAc
"β"-Cholestyl chloride (m. p. 105°)
$SOCl_2$
α-Cholestanol (m. p. 184°)

The observation that the cholestanols (but not cholesterol) yield different chlorides according as they are treated with phosphorus pentachloride or with thionyl chloride was made by Marker.[30]

While the configurational relationships of the saturated chloro compounds to the alcohols have not been determined with certainty, Ruzicka [31] suggested that, since α-cholestanol (*epi*) has a higher melting point than β-cholestanol, the higher melting cholestyl chloride also has the true α(*epi*)-configuration. If this inference proves to be correct, the prefixes *"α"* and *"β"* arbitrarily assigned in the literature to the two cholestyl chlorides will correspond to the true configurations at C_3 referred to that of cholesterol. While the difference in melting point is not great, a comparison of the melting points of several pairs of epimers obtained from the chlorides by degradative reactions offering no opportunity for Walden inversion reveals a definite trend in the same direction.

Melting Points of Epimers

α-Cholestyl chloride	116°	β-Cholestyl chloride	105°
3(α)-Chloro*allo*cholanic acid	176°	3(β)-Chloro*allo*cholanic acid	196°
Methyl ester	128°	Methyl ester	135°
3(α)-Chloro*allo*norcholanic acid	234°	3(β)-Chloro*allo*norcholanic acid	213°
Methyl ester	176°	Methyl ester	159°
α-Chloroandrosterone	173°	β-Chlorandrosterone	128°

The data assembled in the table for the acidic degradation products are taken largely from the paper of Barr, Heilbron and Spring, *J. Chem. Soc.*, 737 (1936); the chloroandrosterones have been studied by various workers (pp. 230, 233). In four of the six cases the α-compound melts at a higher temperature than its epimer, and the average increment for the six pairs is +11°. This general trend in the melting-point characteristics lends definite weight to Ruzicka's assumption. Unfortunately the optical constants are not available for comparison.

If the configurations are as indicated, the reactions represented in the above chart by vertical arrows all proceed without steric rearrangement and those written horizontally involve Walden inversions. According to this interpretation Walden inversions occur in all the metathetical reactions of the unsaturated compounds (cholesterol and cholesteryl chloride), while all of the transformations of the saturated compounds, with the exception of the reactions of the cholestanols with thionyl chloride, proceed without inversion.

Chloroandrostenone (p. 232). The striking observation that this substance (I) can be converted into compounds of the opposite configuration at C_3 (II and III) finds a close parallel in the transformation of cholesteryl chloride (α) into α-cholestanol, by hydrogenation and hydrolysis, and into cholesterol (β), by hydrolysis (p. 392). Since there are indications that in the sterol series a Walden inversion is more likely to occur in the reactions of unsaturated than of saturated compounds, it is probable that the transformation of chloroandrostenone (I) into androsterone (II) through the saturated ketone proceeds without inversion and that an inversion occurs in the direct hydrolysis to III. Chloroandrostenone therefore probably has the α(*epi*)-configuration at C_3, a conclusion which agrees with the observation (p. 233) that it yields on hydrogenation a saturated chloroketone (m.p. 173°) which can be characterized as α-chloroandrosterone (p. 392).

Butenandt and Grosse, *Ber.*, **69**, 2776 (1936), found that chloroandrostenone can be prepared very conveniently from dehydroisoandrosterone by the method developed by Beynon, Heilbron and Spring for the conversion of cholesterol to cholestyl chloride (p. 364). The *p*-toluenesulfonate of the hydroxy compound yields an abnormal methyl ether on alcoholysis in the presence of potassium acetate, and the methoxyl group is easily replaced by halogen on treatment with acid.

Oxidation of Cholesteryl Acetate Dibromide (p. 234). As one by-product in the preparation of dehydroisoandrosterone by the oxidation of cholesteryl acetate dibromide, a number of investigators[42, 43, 47] have isolated 3-hydroxy-Δ^5-cholenic acid. The unsaturated acid was obtained also by Fujii and Matsukawa, *J. Pharm. Soc. Japan*, **56**, 433 (1936), and degraded to 3-hydroxybisnorcholenic acid (II, p. 247). These authors, *ibid.*, **56,** 158 (1936), also report the isolation from the mixture of a substance regarded as somewhat impure Δ^5-pregnenol-3-one-20 (p. 247) as the acetate. Kuwada, *ibid.*, **56,** 75 (1936), isolated a product of over-oxidation which was characterized as 3-hydroxy-Δ^5-aetiobilianic acid by conversion to aetio*allo*bilianic acid (p. 331) [Kuwada and Miyasaka, *ibid.*, **56,** 631 (1936)].

Bio-assay of Hormone Preparations (p. 236). Details and variations of the test method are discussed by Gallagher and F. C. Koch, *J. Pharmacol.*, **55,** 97 (1935), Ramirez and Rivero, *J. Am. Pharm. Assoc.*, **25,** 99 (1936), and Dessau, *Acta Brevia Neerland.*, **5,** 139 (1935). Procedures for the extraction of hormones from urine for biological assay are described by Callow, *Lancet,* II, 565 (1936), and by Gallagher, F. C. Koch and Dorfman, *Proc. Exptl. Biol. Med.*, 33, 440 (1935).

Crystallizates from Testicular Extracts (p. 240). The hormone isolated by Ogata and Hirano[66] has been compared with androstanedione by Hirano, *J. Pharm. Soc. Japan,* **56,** 717 (1936), and found to be quite different from this compound. In a further investigation, Hirano isolated four new substances in amounts varying from 50 mg. to 200 mg. from 50 kg. of hog testes. Substance A, m.p. 258-264°, is assigned the formula $C_{21}H_{32}O_3$ and called **testalolone.** The compound forms an insoluble digitonide, a monobenzoate, and a dioxime; it has the reducing properties of an aldehyde, and the ring system is saturated. From these and other observations, and in analogy with known substances, Hirano provisionally suggests that testalolone is a derivative of 3-hydroxyandrostane with the group $-COCHO$ as a substituent at C_{17}. Substance B, m.p. 95-96°, $C_{19}H_{38}O_3$, has one free hydroxyl group and yields palmitic acid on hydrolysis. The other hydrolysis product gives formaldehyde on treatment with lead tetraacetate. Hirano provisionally regards the new substance as a monopalmitate of propanediol-1,2 and is investigating its possible relationship to Laqueur's X-substance (p. 396). Substance C, m.p. 65-66°, $C_{19}H_{40}O_3$, is called **testriol** and considered to be an open-chain, triatomic alcohol, probably $(CH_3)_2C(OH) \cdot C_{14}H_{28}CH(OH)CH_2OH$. Substance D, m.p. 219-224°, is probably a C_{23}- or C_{24}-compound containing three atoms of oxygen.

Activity of Androsterone and Testosterone Derivatives (p. 240). Much interest has been shown in the preparation and bio-assay of 17-alkyl derivatives of testosterone. Ruzicka[68, 69] found that the methyl derivative can be obtained readily from dehydroisoandrosterone by a process even simpler than that employed for the preparation of testosterone itself (p. 239). The unsaturated hydroxyketone (I, p. 239) is treated with excess Grignard reagent and the resulting diol is oxidized in the form of the dibromide. On debromination, the double bond migrates from the 5,6- to the 4,5-position and 17-methyltestosterone (m.p. 164°) is obtained. Fujii and Matsukawa, *J. Pharm. Soc. Japan,* **55,** 1333 (1935), reported the independent preparation of the compound by the same method. According to most reports, 17-methyltestosterone is about equal in activity to testosterone in the capon test and has a slightly greater activity in the rat test.

While the introduction of a methyl group seems to enhance somewhat the physiological actions of the natural hormone, an ethyl group has the opposite effect and results in a decided loss in activity. The preparation of 17-ethyltestosterone (m.p. 139°) was undertaken by both Butenandt and Ruzicka, and certain difficulties were encountered in applying the standard method [Butenandt, Cobler and Josef Schmidt, *Ber.*, **69,** 448 (1936); Butenandt and Schmidt-Thomé, *ibid.*, **69,** 882 (1936); Ruzicka and Rosenberg, *Helv. Chim. Acta,* **19,** 357 (1936)]. It eventually was recognized in both laboratories that some reduction of the 17-carbonyl group occurs in the course of the reaction of dehydroisoandrosterone (and similar ketones) with ethylmagnesium iodide. No reduction was observed when using the methyl Grignard reagent, while with propylmagnesium iodide reduction predominated over addition. The reduction by the Grignard reagent follows chiefly the same steric course as catalytic hydrogenation, although Ruzicka at first was misled on this point by the difficulty of isolating the unmethylated diol in a pure condition. In the final stage of the process, Butenandt obtained a compound which at first was regarded as the true (Δ^4) 17-ethyltestosterone but which was later found to be the Δ^5-isomer. The conditions of the original debromination evidently were not such as to promote the usual bond migration, but it was found that the Δ^5-compound is isomerized easily by acids (compare p. 359).

Applying the standard synthetic method, Fujii and Matsukawa, *J. Pharm. Soc. Japan,* **56,** 225 (1936), prepared 17-benzyltestosterone (m.p. 225°), while Kuwada and Yago, *ibid.*, **56,** 625 (1936) prepared 17-vinyltestosterone (m.p. 170°) and 17-allyltestosterone (m.p. 137°). Both the vinyl and the allyl compound were found to be about one-third as active as testosterone in the rat test.

From a by-product obtained in the hydrogenation of an intermediate in the preparation of a quantity of testosterone, Ruzicka and Kägi, *Helv. Chim. Acta,* **19,** 842 (1936), were able to prepare an isomer of testosterone having the opposite configuration at C_{17}. It was found that inversion at this position results in a great loss in hormonal activity. Butenandt and Hanisch, *Ber.*, **69,** 2773 (1936), undertook the preparation of the Δ^5-isomer of testosterone and succeeded in obtaining the compound in the form of the acetate by the process of debromination in neutral solution (p. 359). It was not possible, however, to hydrolyze the acetate without rearrangement of the double linkage. Δ^5-Androstenolone acetate was found to be only about one-half as active as testosterone acetate in both the capon and rat tests. Ruzicka and Wettstein, *Helv. Chim. Acta,* **19,** 1141 (1936), prepared a series of esters of testosterone and found that, as the hydrocarbon residue of the ester group is increased in size, the activity measured by the comb growth test falls off while that measured in the rat test increases. The enol diacetate of testosterone is comparable with the monoacetate in androgenic activity and it gives no response in the Allen-Doisy test [Ruzicka and W. H. Fischer, *ibid.*, **19,** 1371 (1936)]. 17-Aminoandrostanol-3(α) (m.p. 187-188°) was prepared by the reduction of androsterone oxime by Ruzicka and Goldberg, *ibid.*, **19,** 107 (1936), and by Marker, *J. Am. Chem. Soc.*, **58,** 480 (1936). Tests showed that the replacement of the hydroxyl group at C_{17} by an amino group results in greatly reduced activity.

The relationship between structure and physiological activity among compounds of the androsterone group has been reviewed recently by Tscherning, *Angew. Chem.*, **49,** 11 (1936), and by Ruzicka, *ibid.*, **49,** 28 (1936); *Helv. Chim. Acta,* **19,** E89 (1936). The biological activities of a number of the compounds have been investigated further by Deanesly and Parkes, *Biochem. J.*, **30,** 291 (1936), Korenchevsky, Dennison and Brovsin, *ibid.*, **30,** 558 (1936), and Korenchevsky and Dennison, *ibid.*, **30,** 1514 (1936).

Activation of Testosterone by the X-Substance (addition to p. 240). It was discovered by Laqueur and co-workers [60] that a substance present in testes and called the X-substance is capable of enhancing greatly the activity of testosterone on seminal vesicles and prostates of castrated rats. The substance is inert when injected alone, but when injected together with testosterone the activity of the latter is amplified from five to ten times. The X-substance serves also as an activator of androsterone and androstanediol [Dingemanse and Polak, *Acta Brevia Neerland.*, **5,** 179 (1935)]. Laqueur characterized the substance as fat-soluble and acidic, and Miescher, Wettstein and Tschopp, *Chemistry and Industry,* **55,** 238 (1936), found that certain higher fatty acids share the property of acting as accessory substances. Palmitic acid is one of the most active and exhibits all the actions of the X-substance. Ricinelaidic, stearic, and elaidic acids showed progressively decreasing potency. Since the fatty oils commonly used as solvents in the bio-assay of male hormones probably contain varying amounts of activators in the form of free fatty acids, the problem of standardization is clearly complicated by this factor. The effectiveness of a hormone varies both with the nature and the amount of the solvent used [Deanesly and Parkes, *Lancet*, I, 837 (1936)].

Oestrogenic Activity of Compounds of the Androsterone Group (addition to p. 240). Following the discovery that androstenedione and dehydroisoandrosterone possess some oestrogenic activity (p. 236), Butenandt, *Naturwissenschaften*, **24**, 15 (1936), found that androstenediol (II, p. 239) combines to a marked degree the physiological properties of male and female hormones. The substance induces oestrus in castrated female mice and promotes comb growth in capons, and it causes the premature development of female as well as male infantile rats. Butenandt found the substance to be active in a total dosage of 4×0.2 mg. in the Allen-Doisy test with mice (1-2 days oestrus). Similar observations concerning androstenediol and its 17-methyl derivative were reported by Tschopp, *Arch. intern. pharmacodynamie*, **52**, 381 (1936) [see also Deanesly and Parkes, *Brit. Med. J.*, **1**, 257 (1936)]. Butenandt and Dannenberg, *Ber.*, **69**, 1158 (1936), prepared Δ^1-androstenedione from 2-bromoandrostanedione-3,17 (compare pp. 249-251) and found that, while the compound has no male hormonal actions, it gives a positive response in the Allen-Doisy test in 4×0.5 mg. dosage. On comparing this substance with Δ^4-androstenedione, a compound comparable in activity with the male hormone androsterone, it is striking that the transposition of the double bond from the 4,5- to the 1,2-position results in a compound having the actions of a follicular hormone. Still other oestrogenic substances of the androsterone group were discovered by Butenandt and B. Riegel, *ibid.*, **69**, 1163 (1936). 6-Ketotestosterone, obtained as the acetate by oxidizing the 17-monoacetate of Δ^5-androstenediol-3,17 with chromic anhydride, gave a positive reaction in the Allen-Doisy test in 4×0.5 mg. dosage. Δ^4-Androstenetrione-3,6,17 has about the same oestrogenic activity.

Marker, O. Kamm, Oakwood and Laucius, *J. Am. Chem. Soc.*, **58**, 1948 (1936), found that a mixture of the epimeric 3-carbethoxyandrosterones gave an oestrous response in rats when administered in quantities of 5-10γ, although no activity in the comb growth test was observed in doses of 2 mg. The mixture of free acids was much less active than the esters. The material was prepared by oxidizing a mixture of epimeric 3-carbomethoxycholestanes obtained by the carbonation of cholesterylmagnesium chloride, followed by hydrogenation and esterification [Marker, Oakwood and Crooks, *ibid.*, **58**, 481 (1936)].

The preparation of a compound of remarkable potency as both a male and female hormone has been reported by Fujii and Matsukawa, *J. Pharm. Soc. Japan*, **56**, 543 (1936). Dehydroisoandrosterone, treated with dry hydrogen chloride, gave 5-chloroisoandrosterone (Ruzicka [68]), from which there was obtained by oxidation and bromination a substance described as 2-bromo-5-chloroandrostanedione. On treatment with potassium acetate and acetic acid this yielded a doubly unsaturated diketone, m.p. 168°, regarded as Δ^1-dehydro-Δ^4-androstenedione-3,17. The capon unit reported for the compound is about equal to that of androsterone, and it was found that the injection of 0.5 mg. of material in four doses into a castrated mouse gave a positive Allen-Doisy test.

Stereochemical Nomenclature (addition to p. 240). According to the proposal of Ruzicka (p. 116), the steric arrangement of a substituent at the 3-position is indicated by a prefix, cis or trans, to express the conventionally assumed relationship of the group to the hydrogen atom at C_5. In this system androsterone (II, p. 228) and isoandrosterone (I, p. 228) are 3-cis and 3-trans compounds, respectively. In the case of unsaturated sterols having no hydrogen at C_5, the arrangement of the group at C_3 is referred to that of the corresponding product of hydrogenation. Dehydroisoandrosterone, for example, is designated trans because in the hydrogenation product the substituents at 3 and 5 are assumed by convention to have this relationship (p. 233, note 39). Although Ruzicka's proposal has been accepted by a number of authors, Schoenheimer and Evans, *J. Biol. Chem.*, **114,** 567 (1936), have criticized the system on the ground that the hydrogen atom at C_5 is not a very satisfactory point of reference even in the saturated sterols, since it is not fixed for all known compounds. The two broad classes of steroids derived from cholestane and from coprostane have opposite configurations at C_5, and an awkward situation arises in the case of isomers such as dihydrocholesterol and coprosterol (p. 116). Considering the assumed relationship of the groups at C_3 and C_5, the substances are designated 3-trans and 3-cis, respectively, and yet the arrangement of the hydroxyl group at C_3 in each case corresponds to that of cholesterol and both compounds are precipitable with digitonin. In order to avoid this difficulty, Schoenheimer and Evans proposed that the steric arrangement of the hydroxyl group should be described in terms of its relationship to the methyl group at C_{10} [see also Lettré, *Ber.*, **68,** 766 (1935)]. According to this system, dihydrocholesterol and coprosterol are both 3-cis compounds, while their epimers are designated 3-trans. This scheme has the advantage of affording a ready distinction, at least with the commoner substances, between sterols which form insoluble digitonides and those which do not. The choice of the C_{10}-methyl group as a fixed point of reference, however, is not without objection. Although the stereochemical relationship of this group to the rest of the molecule is the same in a great many of the known sterols and sterol derivatives, there are definite indications in the work of Dimroth on lumisterol (p. 375) that in the case of the irradiation products of ergosterol the configuration at C_{10} is the opposite of that of the natural sterols. The new proposal therefore does not avoid entirely one serious difficulty of Ruzicka's system even as applied to such compounds as are known at the present time, and provision for new compounds is definitely lacking. It is questionable if any single center of asymmetry in the molecule can provide a rational reference point for defining the configurations at other centers.

A further serious objection to the above proposals is that the steric relationship of the C_3-hydroxyl to the C_5-hydrogen atom or to the methyl group at C_{10} is still uncertain. Ruzicka's assumption that the substituents at C_3 and C_5 in dihydrocholesterol are located on opposite sides of the general plane of the rings may be correct, but it is by no means established. As a provisional convention for purposes of formulation until the matter can be settled, his plan of representing the one valence by a full line and the other by a dotted line is very useful, but the arbitrary and uncertain nature of the assumption should not be lost sight of, and it appears definitely inadvisable to incorporate into the system of nomenclature an assumption which may prove to be incorrect. Even when secure evidence of the configurations becomes available it is questionable if the relationship between centers of asymmetry such as C_3 and C_{10} should be defined by the terms cis and trans, for these prefixes most commonly refer to adjacent centers and bear definite implications regarding steric hindrance and the opportunity for ring formation. Probably a new set of prefixes, and one capable of defining the relationship of each asymmetric carbon atom to the molecule as a whole, would be more appropriate.

As for the arrangement of the characteristic hydroxyl group of the sterols, evidently it is the relationship of this group to the central plane of the ring system which is of prime importance, and this relationship, although unknown, can be defined accurately and adequately by reference to cholesterol. The configuration at C_3 common to cholesterol, dihydrocholesterol, coprosterol, ergosterol and similar steroids is appropriately designated where necessary by the classical prefix β, while the epimers of these substances are $3(\alpha)$-hydroxy compounds, as are the bile acids and androsterone. No arbitrary assumptions are involved in this nomenclature, the facts regarding precipitability with digitonin find a satisfactory correlation, and the standard convention can be retained in writing formulas until final evidence becomes available. For natural products, the common names usually are entirely adequate, and usually it is possible with the use of the prefixes α and β, and sometimes iso, to assign satisfactory names to their derivatives and to related compounds. For purposes of specific reference to the configuration at C_3, androsterone may be called α-androsterone, since it corresponds to α-cholestanol (*epi*dihydrocholesterol). The companion substance isolated from urine was named "dehydroandrosterone" at a time when there was no reason to suppose that a Walden inversion occurs in one of two similar hydrolysis reactions (pp. 232-233). Since it is now known that the steric arrangement at C_3 is the opposite of that of androsterone, the original name is recognized as misleading. The substance is derived from the diastereomer of androsterone, and hence in this book it has been called dehydroisoandrosterone. An equally acceptable, and perhaps preferable, name for isoandrosterone is β-androsterone, and dehydroisoandrosterone may be called 3(β)-hydroxy-Δ^5-androstenone-17, or Δ^5-androstenol-3(β)-one-17. These names reveal at once the correspondence of the steric arrangement of the hydroxyl group to that of cholesterol. They are as specific as the cis-trans designations, and they imply no assumptions concerning the absolute configurations or a special point of reference.

The proposed system represents only a slight extension of the nomenclature currently employed by most authors who have not adopted cis-trans prefixes in the naming of compounds, and it retains for a key compound of the steroids the classical name β-cholestanol. For the present no drastic revision of tradional names is called for. It is probable, if not certain, that the so-called α- and β-cholestyl halides actually bear the configurational relationship to α- and β-cholestanol implied in the names fortuitously assigned to the compounds (p. 392). Unless the present indications are not sustained by final evidence, the names can be retained. Where the prefixes α and β have been used in assigning provisional names to isomers of unknown structure, as in the case of the ergostenols (p. 371), any possible confusion will vanish as the structures become fully established. Where there is any possibility of confusion with such arbitrary and provisional prefixes, the letter indicating a configurational relationship can be attached to the number. β-Cholestanol, for example, can be given the more specific name cholestanol-3(β).

If the proposed plan of indicating the configuration at C_3 is adopted, it would seem logical to extend the system by the use of a compound such as dihydrocholesterol as a standard, the configuration of all asymmetric centers in the molecule being assigned the designation β. An example of this usage is given in the following section.

Configuration at C_{17} (addition to p. 240). In accordance with the above principles, the saturated diols from androsterone (α) and from isoandrosterone (β) may be called androstanediol-3(α),17 (androstanediol) and androstanediol-3(β),17 (isoandrostanediol). While the diacetate of the 3(β),17-diol on partial hydrolysis yields chiefly the 17-monoacetate,[67] Ruzicka and Goldberg, *Helv. Chim. Acta*, **19**, 99 (1936), found that the diacetate of the epimeric 3(*α*),17-diol gives the 3-monoacetate. A similar observation was made in the case of the Δ^5-unsaturated diols. The greater reactivity of the 3(*β*)-acetoxyl group as compared with the 3(*α*)-group had been observed by Vavon and Jakubowicz, *Bull. soc. chim.*, [4], **53**, 581 (1933), in comparing the esters of *β*- and *α*-cholestanol, and the chief significance of the new results is in the comparison which they afford between groups in positions 3 and 17. The reactivity of an acetoxyl group at C_{17} evidently lies between that of the same group in the two epimeric arrangements at C_3. Ruzicka and Goldberg point out that this order of reactivity is understandable only if it is supposed that the 17-acetoxyl group occupies a trans position with respect to the methyl group at C_{13}. If the substituents on the adjacent carbons 13 and 17 were present in a cis arrangement, the 17-acetoxyl group would be considerably more hindered than a 3-substituent in either the *α*- or *β*-configuration and would tend to survive hydrolysis more effectively in either case. The 17-hydroxyl group of the two diols therefore very probably is present in a trans position with respect to the C_{13}-methyl group.

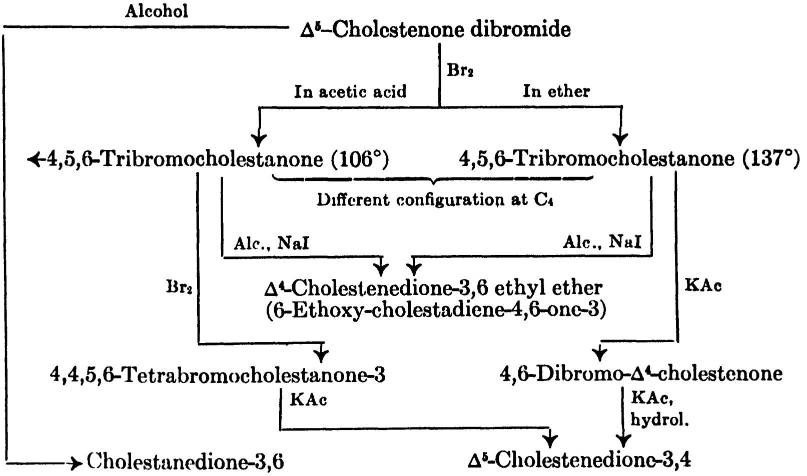
This discovery raises another problem in nomenclature. Although two cis and two trans arrangements are possible for substituents at C_{13} and C_{17}, it is sufficient at present to take account of only one pair of isomers, since the configuration at C_{13} is the same in all natural steroids and an inversion at this position has not been observed. The terms cis and trans furthermore are entirely appropriate to the type of isomerism in question, particularly in view of the nature of the evidence upon which the determination of the configuration is based. For these reasons androstanediol and isoandrostanediol are properly assigned the specific names androstanediol-3(*α*),17(trans) and androstanediol-3(*β*),17(trans). The term trans defines the steric relationship of the functional group in question to the C_{13}-methyl group, a specific point of reference which is not likely to be mistaken and which appears to be fixed for all steroids. Should isomers be discovered in which an inversion has occurred at C_{13}, it might be desirable to define the configuration at C_{13} normal to the natural steroids as of the *β*-type. Androstanediol could be called the 3(*α*),17 (trans C^{β}_{13})-diol, and an inversion at C_{13} would give the 3(*α*),17 (cis C^{α}_{13})-diol. Such an elaboration, however, is not required at present, and indeed cases are rare in which sufficient evidence is available to warrant the indication in the name of the steric arrangement at C_{17}. Where an inversion at C_{17} has been observed but where evidence of the configurations is lacking, the abnormal isomer is adequately distinguished from the normal compound by the prefix iso (see, for example, iso*allo*-pregnanol-3-one-20, p. 249).

Methods of Bio-assay (pp. 241-242). From a comparison of the Corner-Allen and Clauberg methods of assay, it is reported that the accuracy of the former test can be approached by the Clauberg test only if many animals are used and group averages taken. L. E. Young, *Proc. Soc. Exptl. Biol. Med.*, **34,** 96 (1936).

The Two Forms of the Corpus Luteum Hormone (p. 243). While Fels, *Zentr. Gynäkol.*, **59,** 2420 (1935), has reiterated the claim that the the two compounds differ in their biological actions and are structural isomers, Hohlweg and Josef Schmidt, *Klin. Wochschr.*, **15,** 265 (1936), support the view that they are polymorphic crystalline modifications of the same substance and are indistinguishable in their biological effect.

Isolation of Progesterone (p. 245). In later work, Butenandt and U. Westphal, *Ber.*, **69,** 443 (1936), developed a more convenient method for the separation of progesterone and the inactive hydroxyketone (*allo*pregnanolone) which accompanies it. On treating the mixture with chlorosulfonic acid the companion substance alone reacts, and the resulting sulfuric acid ester is separated easily as the sparingly soluble sodium salt ($ROSO_3Na$). The hydroxyketone is subsequently recovered by acid hydrolysis. This convenient method of separation greatly facilitates the purification of both compounds, and no other companion substances were discovered in the extracts. W. M. Allen and Goetsch, *J. Biol. Chem.*, **116,** 653 (1936), have described an improved procedure for the extraction of progesterone from pig ovaries whereby 25% of the hormone present in the tissue may be recovered in a pure state.

Bromination of Δ^5-Cholestenone Dibromide (p. 250). The action of bromine on Δ^5-cholestenone dibromide, the oxidation product of cholesterol dibromide, has been studied extensively by Inhoffen, *Ber.*, **69,** 1134, 1702, 2141 (1936), and by Butenandt and Schramm, *ibid.*, **69,** 2289 (1936). As monobromination occurs at position 4 rather than 2 it is assumed that the dibromide is of the coprostane series (A/B:cis). A striking observation is that the bromine atom introduced at C_4 assumes different steric arrangements when the bromination is conducted in glacial acetic acid (Butenandt) or in ether (Inhoffen). A few of the many interesting transformations noted in the course of characterizing the isomeric tribromo ketones are indicated in the chart on the opposite page. Bromination of the lower melting tribromo ketone results in the introduction of an additional atom of bromine at the 4-position, and the resulting tetrabromide on treatment with potassium acetate yields Δ^5-cholestenedione-3,4, a compound which can be obtained also from the higher melting tribromo ketone and which is capable of functioning in an enolic form. Both tribromo ketones are converted by alcohol and sodium iodide into an enol ether of Δ^4-cholestenedione-3,6 which


Alcohol
Δ⁵-Cholestenone dibromide
Br₂
In acetic acid
In ether
4,5,6-Tribromocholestanone (106°)
4,5,6-Tribromocholestanone (137°)
Different configuration at C₄
Alc., NaI
Alc., NaI
Br₂
Δ⁴-Cholestenedione-3,6 ethyl ether
(6-Ethoxy-cholestadiene-4,6-one-3)
KAc
4,4,5,6-Tetrabromocholestanone-3
4,6-Dibromo-Δ⁴-cholestenone
KAc
KAc, hydrol.
Cholestanedione-3,6
Δ⁵-Cholestenedione-3,4

Windaus, *Ber.*, 39, 2249 (1906), had obtained by warming the unsaturated diketone with alcoholic hydrochloric acid. The conversion of Δ^5-cholestenone dibromide into cholestanedione-3,6 with boiling alcohol was observed by Urushibara and Ando, *Bull. Chem. Soc. Japan*, **11,** 434 (1936), Ruzicka, Bosshard, W. H. Fisher and Wirz, *Helv. Chim. Acta*, **19,** 1147 (1936), and Fujii and Matsukawa, *J. Pharm. Soc. Japan*, **56,** 642 (1936). The reactions often proceed through various intermediate stages, and interesting interpretations involving assumed or established additions, eliminations, hydrolyses, and allylic shifts are suggested in the original articles. Further observations concerning polybromo derivatives of cholestenone, cholestanone, and coprostanone are reported by Ruzicka (*loc. cit.*) and by Butenandt, Schramm, Wolff and Kudszus, *Ber.*, 69, 2779 (1936). Dane, Wang and Schulte, *Z. physiol. Chem.*, 245, 80 (1936), also investigated the bromination of cholestenone (and of 3-ketocholanic acid) and introduced a useful new method for effecting the elimination of hydrogen bromide. 6-Bromo-Δ^4-cholestenone was converted into $\Delta^{4,6}$-cholestadienone by the action of silver nitrate in pyridine solution at room temperature. The interesting 3-keto-Δ^4-cholenic acid (pp. 255, 370) was prepared by these investigators through 3-keto-4-bromocholanic acid.

In the course of his work, Inhoffen observed that cholestenone (Δ^4) is converted by bromine in the presence of hydrogen bromide into 4,6-dibromo-Δ^4-cholestenone, a reaction which he interpreted as proceeding through the enol form, cholestadiene-3,5-ol-3, produced by the isomerization of cholestenone under the catalytic influence of hydrogen bromide. This view was substantiated in an investigation of the bromination of a cholestenone enol acetate first prepared by Ruzicka and W. H. Fischer, *Helv. Chim. Acta*, **19**, 806 (1936), and formulated as a $\Delta^{2,4}$- or $\Delta^{1,3}$-compound. Inhoffen's observations point to the $\Delta^{3,5}$-structure.

Epi*allo*pregnanol-3-one-20 (addition to p. 250). This substance, which differs from *allo*pregnanol-3-one-20 (formula XV, p. 249) only in the steric arrangement of the hydroxyl group at C_3, was isolated from the sterol fraction of 10,000 gallons of human pregnancy urine by Marker, O. Kamm and McGrew, *J. Am. Chem. Soc.*, paper IX, in press. The carbinols were separated from non-carbinol material as the sodium salts of the half-esters of phthalic acid, and the ketonic fraction was separated with the use of Girard's reagent. The *epiallo*pregnanol-3-one-20 isolated amounted to 1-2 mg. per gallon of urine. The compound melts at 162-164°, it is not precipitable with digitonin, and it yields *allo*pregnanedione on oxidation. The new substance occupies an interesting place in the genetic series of substances listed on page 252. As a probable reduction product of the unsaturated ketone progesterone, it is comparable with androsterone with regard to the configuration at C_3, and has the configuration at C_5 of *allo*pregnanol-3-one-20.

Correlation of Progesterone with Androsterone (addition to p. 250). By the conversion of *allo*pregnanediol, a reduction product of progesterone, into androstanedione, an oxidation product of androsterone, Marker, O. Kamm, D. M. Jones and Oakwood, *J. Am. Chem. Soc.*, paper VIII, in press, established a relationship between the two hormones.

Specificity of Progesterone (pp. 250-251). Like the Δ^1-isomer (II), Δ^5-pregnenedione-3,20 has no progestational activity. It is remarkable that, although the Δ^5-isomer can be isomerized to progesterone with great ease under the influence of acid catalysts, this change apparently does not occur in the organism under the conditions of the test. The β,γ-unsaturated isomer of progesterone was prepared by debromination of the dibromide in neutral solution (compare p. 359). U. Westphal and Schmidt-Thomé, *Ber.*, **69**, 889 (1936). [For a review, see U. Westphal, *Ergeb. Physiol. exp. Pharmakol.*, **37**, 295 (1935)].

While many compounds closely related to progesterone in structure do not appear to share the specific physiological properties of the hormone, Klein and Parkes, *Chemistry and Industry*, **55**, 236 (1936), reported that certain of the androgenic compounds prepared by Ruzicka elicit typical progestational proliferation of the endometrium. Testosterone itself gave a partial proliferation in a dose of 20 mg. According to a citation of Ruzicka and Rosenberg, *Helv. Chim. Acta*, **19**, 357 (1936), 17-methyltestosterone is the most active compound of the group, and in a dosage of 7 mg. has an action equal to that of 1 mg. of progesterone. Progesterone, on the other hand, has no effect on the comb growth of capons [Albrieux, Buño, Engel and Morató-Manaro, *Klin. Wochschr.*, **15,** 206 (1936)].

Origin of the Oestrogenic Hormones (p. 255). In an attempt to test the hypothesis that the oestrogenic agents present in the organism result from the degradation of cholesterol, Rondoni, Carminati and Corbellini, *Z. physiol. Chem.*, **241,** 71 (1936), allowed mixtures of cholesterol (10 g.) and minced liver (200 g.) to autolyze for several weeks at temperatures from 37 to 53°. In tests made with benzene extracts, nearly all of the mixtures were found to have oestrogenic activity. H. E. Voss and Rabald, *ibid.*, **245,** 76 (1936), however, reported that in conducting similar experiments they had found the commercial cholesterol employed to have sufficient oestrogenic activity to account for the positive results obtained. [See also Rondoni, *ibid.*, **245,** 78 (1936)].

Origin and Metabolism of Cholesterol (p. 255). Evidence that coprostanone is not an intermediate in the hypothetical conversion of cholesterol into bile acids in the animal organism has been presented by Schoenheimer, Rittenberg, Berg and Rousselot, *J. Biol. Chem.*, **115,** 635 (1936). Dogs with bile fistulas were injected intravenously with an emulsion of coprostanone-4,5d_2 (p. 123) and the fistula bile subsequently collected was examined for the presence of deuterium. It was found that although some of the injected material had passed through the liver this organ had not utilized the sterol derivative in the formation of cholic acid, the cholic acid isolated containing no detectable amount of deuterium. Similar experiments with unsaturated ketones and keto acids would be of the greatest interest.

In considering the origin of cholesterol in the body, Windaus [quoted by H. Lettré and H. H. Inhoffen, "Uber Sterine, Gallensäuren, u. verw. Naturstoffe," p. 103 (1936)] has offered the conjecture that the four-ring system comes from oleic acid, through civetone, the angular methyl groups being supplied in a reaction with formaldehyde. A relation between sterol synthesis and fat metabolism in plants is suggested by the observation of MacLachlan, *J. Biol. Chem.*, **113,** 197 (1936), that as germination in soy beans progresses there is a diminution in the total fats present and an increase in the sterol content. In studying fat metabolism in the animal organism, Schoenheimer and Rittenberg, *ibid.*, **114,** 381 (1936), found with the use of heavy water that in living mice fatty acids are continuously destroyed and replaced, even in fat depots, the acids almost certainly being formed by synthesis from carbohydrates of the diet. They also demonstrated experimentally that desaturation of fatty acids can occur in the living organism [*Idem, ibid.*, **113,** 505 (1936)].

Anchel and Schoenheimer, *J. Biol. Chem.*, **114,** 539 (1936), note that the presence of cholestenone as an intermediate product of metabolism is further suggested by the observation that unsaponifiable material from arteriosclerotic aortas gives an absorption spectrum characteristic of α,β-unsaturated ketones.

Crystalline Substances from the Adrenal Cortex (addition to p. 255). Since the discovery [Rogoff and G. N. Stewart, *J. Am. Med. Assocn.*, **92,** 1569 (1929); Swingle and Pfiffner, *Science*, **71,** 321 (1930)] that the life span of adrenalectomized dogs can be prolonged by administration of an extract of the adrenal cortex, attempts have been made by various investigators to isolate the active hormone or hormones ("cortin"). The dog method of assay unfortunately is subject to serious limitations, which is true also of the adrenalectomized-dog muscle test of Everse and de Fremery, *Acta Brevia Neerland.*, **2,** 152 (1932), and indeed no really satisfactory biological test is as yet available for the evaluation of cortical hormone concentrates. The difficulties inherent in the problem of isolation are greatly augmented by the inadequacy of the biological control, and progress consequently has been slow. Careful fractionations of extracts of adrenal glands have been rewarded by the isolation of a number of crystalline substances, but these all have proved to be physiologically inactive, or at the most of low and questionable activity, when tested in adrenalectomized dogs. The substances nevertheless are of considerable interest, for they are closely related in structure to the male sex hormones.

The chemical studies have been conducted by three groups of investigators, the principal papers being as follows: Pfiffner, Wintersteiner and Vars, *J. Biol. Chem.*, **111,** 585 (1935); Wintersteiner and Pfiffner, *ibid.*, **111,** 599 (1935); **116,** 291 (1936); Reichstein, *Helv. Chim. Acta*, **19,** 29, 223, 402, 979, 1107 (1936); Mason, Myers and Kendall, *J. Biol. Chem.*, **114,** 613 (1936); **116,** 267 (1936). Both Wintersteiner and Reichstein made extensive use of Girard's reagent in separating ketonic from non-ketonic material and in differentiating between ketones of varying degree of reactivity. Several compounds were isolated in independent work in each of the three laboratories, and these are known for the most part by the three sets of serial letters originally assigned to them. While some of the compounds of Wintersteiner and of Reichstein have been identified by direct comparison, and while the correspondence of other substances seems probable, the literature on the subject is at present in a state of some confusion. For this reason and because the formulas and structures are still uncertain in some respects, this review will be limited to the citation of a few of the more important observations.

By suitable methods of oxidation, Reichstein was able to convert his substances A, C, and D into the same saturated diketone, m.p. 178°, of the probable formula $C_{19}H_{26}O_3$. His compounds E and F similarly yielded the unsaturated diketone adrenosterone (m.p. 224°, $C_{19}H_{24}O_3$), which had been isolated from the cortical extracts. Subsequently adrenosterone was found to yield the saturated diketone (178°) on hydrogenation and consequently all six compounds are now correlated. Since the analytical data and the ketonic character of the substances suggested a relationship to members of the androsterone group, Reichstein investigated the action of the saturated and unsaturated diketones in promoting the comb growth of capons and made the striking discovery that they both possess strong male sex hormone activity, being about one-third and one-fifth as active as androsterone. A similar observation was made by Kendall and co-workers concerning a diketone very similar to adrenosterone and possibly identical with Reichstein's substance. Finally Reichstein proved the suspected relationship to androstanedione and androstenedione by the conversion of the saturated diketone (178°) into androstane and into androstanone-17. One of the carbonyl groups of the diketone is evidently located at C_{17}, and, since a related hydroxyketone of the series is precipitated by digitonin, the second group probably is situated at the 3-position. According to Reichstein's observations, the saturated diketone differs from androstanedione-3,17 by only one additional atom of oxygen, which is present in some unreactive combination. The substance liberated no gas in the Zerewitinoff test and only two carbonyl groups could be detected with certainty. It seems possible that the oxygen atom is present either in oxidic combination, in a carbonyl group occupying a hindered position (C_{11}, C_{18}), or in the form of an unresponsive tertiary hydroxyl group (C_8, C_9). Adrenosterone is an α,β-unsaturated ketone, probably the Δ^4-dehydro derivative of the saturated diketone (178°).

Of the other compounds which Reichstein has shown to have the androstane ring system with substituents at 3 and 17 and with an unlocated oxygen atom, two have a saturated ring system hydroxylated at C_3 and two are α,β-unsaturated ketones related to adrenosterone. They are all C_{21}-compounds and have the carbon skeleton characteristic of pregnane or progesterone, a two-carbon group being situated at C_{17}. From present indications the probable structures may be defined further as follows: Reichstein's compound A (Wintersteiner's A, probably Kendall's D), $C_{21}H_{34\text{-}36}O_5$, has a saturated nucleus, a C_3-hydroxyl, an unlocated oxygen, and carries at C_{17} a hydroxyl group and the group $-CH(OH)CH_2OH$. Reichstein's C (Wintersteiner's D) and D are stereoisomers differing from A only in that the side chain is $-COCH_2OH$. Reichstein's F (Wintersteiner's F, probably Kendall's E), $C_{21}H_{28\text{-}30}O_5$, is an α,β-unsaturated ketone with the carbonyl group at C_3 and the double bond at C_4-C_5, and the substituents at C_{17} are hydroxyl and —$COCH_2OH$. One oxygen atom is unlocated. From the results of the Zerewitinoff test, Kendall was led to believe that the extra oxygen is present as a tertiary hydroxyl group, but Reichstein has pointed out that the methane liberated may be due to enolization and that a similar result was not obtained with his saturated diketone (178°). The compound E of Reichstein differs from F only in having the side chain —$CH(OH)CH_2OH$.

Chapter VI

New Glycoside (addition to p. 259). From the seeds of *Strophanthus emini*, Lamb and S. Smith, *J. Chem. Soc.*, 442 (1936), isolated after partial enzymatic hydrolysis the monoside **emicymarin,** $C_{30}H_{46}O_9$. On acid hydrolysis this yielded trianhydroperiplogenin and digitalose.

Oxidation of Strophanthidinic Acid (p. 264.) Elderfield, *J. Biol. Chem.*, **113,** 631 (1936), has shown in a reinterpretation of earlier work of Jacobs, *ibid.*, **57,** 553 (1923), that when the lactone ring of strophanthidinic acid is saponified and the compound oxidized in alkaline solution with permanganate, the side chain is degraded to $-COCOOH$. The acid group lactonizes with the hydroxyl group at C_{14} and the product of the reaction is an α-keto lactone acid of the formula $C_{21}H_{30}O_8$ (previously $C_{23}H_{30}O_8$).

Zerewitinoff Determination (p. 265). From the results of tests made with a number of aglycone derivatives, Jacobs concluded that the active hydrogen atom of the lactone ring invariably gives one mole of methane with the Grignard reagent [Jacobs and Collins,[21] Jacobs and Gustus, *J. Biol. Chem.*, **74,** 811 (1927)]. Tschesche and Haupt, *Ber.*, **69,** 459 (1936), questioned the validity of this generalization, for they observed no evolution of gas in a test with anhydrouzarigenin benzoate. They reported also an apparently anomalous result with anhydroconvallotoxigenin benzoate, but the interpretation in this case is questionable (see p. 417. Jacobs and Elderfield, *ibid.*, **114,** 597 (1936), subsequently examined a number of additional substances and found that usually the active hydrogen atom responsible for the Legal reaction liberates a full mole of gas, although in a few cases there was a deficiency of 40-60% in the quantity of methane.

Colorimetric Determination of Molecular Weight (p. 265). Observing that cardiac glycosides and aglycones having an active hydrogen in the unsaturated lactone ring give with alkaline picric acid solution a characteristic orange-red color, Neumann, *Z. physiol. Chem.*, **240,** 241 (1936), developed a colorimetric method for the quantitative determination of substances of this group. By comparing the color readings of a solution of a cardiac compound with a calibration curve obtained with k-strophanthidin, a few milligrams of material can be determined with a high degree of accuracy. The colorimetric method can be used for the determination of the molecular weight of substances having the characteristic β,γ-unsaturated lactone ring.

Dehydration of *Epi*allocholesterol (p. 282). See p. 362.

Digoxigenin (p. 283). In a paper published almost simultaneously with the first edition of this book, Tschesche and Bohle, *Ber.*, **69,** 793 (1936), on the basis of new experimental evidence, arrived at a formula for digoxigenin identical with that suggested by the author from other considerations. Tschesche and Bohle established the skeletal structure of the aglycone and proved that it belongs to the coprostane series (A/B :cis) by degradation through the anhydro compound, the tetrahydroanhydro compound, and the diketone (m.p. 290°) to a saturated desoxylactone identical with a lactone obtained from digitoxigenin by Windaus and Stein.[44] On oxidizing the diketone (tetrahydroanhydrodigoxigenone) one of the rings was opened. As the resulting dibasic keto acid gave a diketone on pyrolysis, the ring in question must be ring A and consequently one of the original secondary hydroxyl groups is located in this ring, probably at C_3. Tschesche and Bohle noted that the other secondary hydroxyl group can hardly be in ring A, for it then would be involved in the oxidative opening of this ring. The 6-position also is unlikely, for the dibasic keto acid does not have the properties of a β-keto acid. Positions 15 and 16 can be eliminated because the anhydro linkage of anhydrodigoxigenone would in either case be conjugated with a carbonyl group and the unsaturated diketone would show selective ultraviolet absorption, which is not the case. The anhydro linkage doubtless would migrate to a position of conjugation with a carbonyl group at C_7, and hence this position also is unlikely. Of the remaining positions, 11 and 12, only the former location accounts for the observation that the saturated diketone is isomerized, at least partially, by alkali. A carbonyl group at C_{11}, but not at C_{12}, would be adjacent to an asymmetric carbon carrying a hydrogen atom. In this way Tschesche and Bohle reached the conclusion that the secondary hydroxyl group in question very probably is located at C_{11}, as was inferred by the author from an entirely different set of facts (p. 283).

S. Smith, *J. Chem. Soc.*, 354 (1936), succeeded in isolating two monoanhydro derivatives of digoxigenin similar to the isomeric compounds which he had obtained previously from digitoxigenin [*ibid.*, 1050 (1935)]. The compounds very probably have the expected $\Delta^{14,15}$ and $\Delta^{8,14}$ structures. One isomer, m.p. 182°, was obtained in a pure condition by crystallization of the mixture of substances resulting from the action of dilute acids on digoxigenin. When this isomer was dissolved in concentrated hydrochloric acid at 10°, an unstable chloro compound was formed and separated in a crystalline condition. On treatment with water, the chloro compound was rapidly decomposed and the second anhydrodigoxigenin, m.p. 192°, was formed. The method of effecting the isomerization seems to be generally applicable. Probably the migration of the double bond to an adjacent position is the result of the addition and elimination of hydrogen chloride (compare α- and β-ergostenol, p. 372).

Sarmentogenin (addition to p. 283). Jacobs and Heidelberger[6] characterized this aglycone from sarmentocymarin (m.p. 137°) as a trihydroxy unsaturated lactone of the composition $C_{23}H_{34}O_5$. They prepared anhydro-, iso-, and dihydro-sarmentogenin by the usual methods, and also found that the aglycone on benzoylation in pyridine solution forms a dibenzoate. Jacobs and Heidelberger also reported, without comment, the striking observation that only one of the two groups involved in the benzoylation reaction was attacked in an oxidation experiment, the product having the composition of a monoketone and giving a monosemicarbazone. (The composition is sufficiently close to that of a diketone to suggest that the compound may have two carbonyl groups, one of them being inert.) In a recent investigation Tschesche and Bohle, *Ber.*, **69**, 2497 (1936) [see also Tschesche, *ibid.*, **68**, 423 (1935)], discovered still more definite indications that one of the secondary hydroxyl groups of sarmentogenin occupies a hindered position in the molecule and is similar in this respect to the C_{11}-hydroxyl group of the isomeric aglycone digoxigenin (p. 283). In fact Tschesche and Bohle found that sarmentogenin and digoxigenin have the same structure and differ only in the configuration at C_9. The correspondence of the skeletal structures was established by the conversion of both substances to the same degradation product. Sarmentogenin yields two anhydro compounds, α (m.p. 208°) and β (m.p. 243°), and the first of these on hydrogenation gave a tetrahydroanhydro compound (α_1 and α_2 mixture). On oxidation there was obtained a diketone (α_1, m.p. 270°) which was converted into a monoketone (α_1 and α_2) on reduction by the Clemmensen method. The reduction could not be pushed beyond this point and it is now recognized that the inert carbonyl group is located at C_{11}. Evidence that the group eliminated is located at C_3 was found in a separate experiment involving the opening of ring A and the formation of a pyroketone. In order to remove the oxygen atom at C_{11}, the ketonic group was reduced catalytically and the alcohol was dehydrated to the $\Delta^{9,11}$-dehydrolactone. On hydrogenation there was obtained a saturated desoxylactone identical with that prepared from both digitoxigenin (Windaus and Stein[44]) and digoxigenin (Tschesche and Bohle, see above). It was established that an inversion at C_9 occurs in the course of the degradation of either sarmentogenin or digoxigenin by the preparation from digoxigenin of a $\Delta^{9,11}$-dehydrolactone identical with that from sarmentogenin (by partial reduction of the 3,11-diketone, hydrogenation to an alcohol, and dehydration). This affords additional evidence of the location of a hydroxyl group at C_{11} in sarmentogenin, as in digoxigenin, and shows that the two aglycones have opposite configurations at C_9. From the present evidence it is probable, if not entirely certain, that the original C_9-configuration of digoxigenin is retained throughout the degradation, while that of sarmentogenin is retained until the asymmetry at C_9 is destroyed in the formation of the $\Delta^{9,11}$-dehydrolactone. The compounds having a carbonyl group adjacent to the asymmetric center offer opportunity for inversion, but isomerization does not appear to occur. Since digoxigenin is obtained from plants containing the glycosides digitoxin and gitoxin, and since these companion substances have the configuration at C_5 normal to the sterols and most steroids, Tschesche and Bohle think it probable that digoxigenin has the normal configuration in which rings B and C are linked in the trans arrangement. Sarmentogin probably represents a rare type of compound having the B/C:cis linkage. This arrangement apparently results in increased steric hindrance at the 11-position. In the digoxigenin series a carbonyl group at C_{11} is reduced with some difficulty, but with the sarmentogenin compounds the reduction is completely blocked. A corresponding reaction with ketonic reagents occurs in the case of anhydrodigoxigenone, if not with digoxigenone or with tetrahydroanhydrodigoxigenone, but none of the ketones of the sarmentogenin series enter into condensations involving the carbonyl group at C_{11}. Another striking observation is that the saturated alcohol having a lone hydroxyl group at C_{11} fails to react with benzoyl chloride in pyridine solution. A further point of general interest is the observation of Tschesche and Bohle that the $\Delta^{9,11}$-dehydrolactone can be hydrogenated in glacial acetic acid solution but not in a neutral alcoholic medium. The double bond extending to the bridge head appears to be comparatively inert.

It is of interest to compare the cardiac activities of the glycosides, sarmentocymarin and digoxin, the aglycones of which differ only in the configuration at C_9. [The results for digoxin are given by K. K. Chen, A. L. Chen and R. C. Anderson, *J. Am. Pharm. Assoc.*, **25**, 579 (1936), while the data for sarmentocymarin were kindly communicated to the author by Dr. K. K. Chen].

Minimal Systolic Dosage

	Configuration at C_9, B/C	Cat unit, mg. per kg.	Frog dose, mg. per g.
Sarmentocymarin	cis	0.21	0.00545
Digoxin	trans	0.22	0.00250

Digoxin contains three sugar units of a type easily eliminated on hydrolysis (2-desoxy sugar), while sarmentocymarin contains but one monose unit, which is resistant to hydrolysis. If differences in the glycosidic part of the molecule are of minor consequence, the results indicate that an inversion at C_9 does not influence the cardiotonic potency to a very marked extent. On the weight basis the two glycosides are of about the same activity according to the cat unit, while digoxin is about twice as potent as the other substance in the frog test. Since the molecular weight of digoxin is nearly one and one-half times that of sarmentocymarin, a comparison of the substances on the basis of the effective aglycone content would indicate a still greater relative activity for digoxin in the frog test and greater potency in the cat test. The differences, although not great, probably are significant and it is interesting that the substance regarded as having the more normal steric arrangement of rings B and C (trans) is definitely more active than the other compound.

Oxidation of Anhydrodihydrostrophanthidin (pp. 285-286). While the oxidation of anhydrodihydrostrophanthidin (I) with permanganate in alkaline solution results in the hydroxylation of the anhydro linkage at C_{14}-C_{15} (and oxidation of the aldehydic group), Jacobs and Elderfield, *J. Biol. Chem.*, **113**, 611 (1936), found that the reaction takes a different course when permanganate is employed in acetic acid solution. In this case the aldehydic group is attacked as before and an oxido group is introduced between positions 8 and 14. When anhydrodihydrostrophanthidin is oxidized with perbenzoic acid in chloroform solution an 8,14-oxide is similarly produced. The structures of the oxides were established beyond question by a number of transformations, and the same remarkable difference in the course of the oxidation with permanganate in alkaline and in acidic solution was noted with other anhydro aglycones. Since the one reaction indicates that the double bond occupies the 14,15-position while the other points to its location at the 8,14-position, Jacobs and Elderfield concluded that anhydrodihydrostrophanthidin and similar compounds probably exist in solution in both the $\Delta^{14,15}$ and the $\Delta^{8,14}$ forms and that the acidity of the medium determines their relative abundance or reactivity. Isomeric anhydro compounds of this type have been isolated from uzarigenin (p. 284), digitoxigenin (p. 410), digoxigenin (p. 409), and sarmentogenin (p. 410), and it would be of interest to compare the action of oxidizing agents on a pair of such isomers.

Configuration of Strophanthidin (p. 290). Jacobs and Elderfield, *J. Biol. Chem.*, **113,** 625 (1936), submitted dihydrostrophanthidin to the cyanohydrin synthesis and in this way transformed the aldehydic group at C_{10} into $-\overset{*}{C}H(OH)COOH$. The acid is not stable in the free condition but combines with the tertiary hydroxyl group at C_5 to form two stereoisomeric homolactones differing only in the configuration at the new center of asymmetry produced in the synthesis. The nature of the isomerism and the location of the lactone linkage was fully established by suitable transformations. Tschesche and Bohle, *Ber.*, **69,** 2443 (1936), have pointed out that a five-membered lactone ring extending between positions 5 and 10 is possible for a cis decalin, but not a trans decalin, type and consequently that strophanthidin must belong to the coprostane series (A/B:cis), like digitoxigenin and gitoxigenin. The correlation of periplogenin with strophanthidin shows that this aglycone also has the cis linkage between rings A and B, and from evidence to be presented below it is now clear that the same is true of digoxigenin, sarmentogenin, and thevetigenin. Uzarigenin is the only aglycone known to have the A/B: trans configuration.

Ouabain (pp. 290-295). The interpretation of the structure and reactions of ouabain presented in the first edition has received some support from an observation of Fieser and Newman, *J. Biol. Chem.*, **114,** 705 (1936), concerning the acetyltrianhydrolactone (VI, p. 294) from isoouabain. As stated on page 294, the validity of the suggested interpretation hinges on the question of whether or not the three nuclear double bonds of the above lactone and of similar degradation products are present in a single, benzenoid nucleus. As the most reliable means of deciding this subtle point in comparable cases is from the absorption spectrum, this method was applied. It was found that the absorption spectrum of the lactone VI is very similar to those of neoergosterol (I, p. 177) and dihydrotrianhydrostrophanthidin (see p. 274). In both of the latter compounds ring B is regarded as aromatic. The absorption maximum of 270 mμ found for the lactone VI is, according to available evidence, characteristic of a benzenoid ring. Perhaps the most pertinent example of a compound having a triene system distributed in more than one ring is dehydroergosterol (p. 175) which shows an absorption maximum at 320 mμ.

The acetyltrianhydrolactone from isoouabain was found to react only slowly with perbenzoic acid and to consume less reagent than would be expected for a non-benzenoid triene. It was pointed out further that the observation of Jacobs and Bigelow that the lactone can be hydrogenated in acetic acid solution, but resists hydrogenation in neutral solvents, finds a close parallel in Dirscherl's findings concerning the nuclear hydrogenation of oestrone (p. 384).

The conclusion that the acetolysis results in the aromatization of ring B has been confirmed by Tschesche and Haupt, *Ber.*, **70,** 43 (1937), by the determination of the absorption spectrum of the lactone $C_{22}H_{28}O_3$ from ouabain. As attempts to aromatize ring A of the methyl ether of this compound by dehydrogenation with platinum were unsuccessful, and because the lactone yields a ketone[72,76] which, unlike β-tetralone, is not sensitive to acid oxidation, these investigators have questioned the validity of the formulation for ring A suggested by the author for the degradation products. They note further that the tentative formula suggested for ouabain (I, p. 292) should be revised in the light of recent information (see below) by transposing the sugar residue to the 3-position.

Thevetin (addition to p. 299). In 1933 Chen and Chen[84] isolated the crystalline heart poison thevetin from be-still nuts, the fruit of the plant *Thevetia neriifolia* found in the Hawaiian Islands, South America, and India. Attempts to determine the empirical formula by analysis led to conflicting views,[84] and unusual difficulties were encountered by Elderfield, *ibid.*, **115,** 247 (1936), in attempting to prepare sugar-free derivatives of the glycoside. The whole problem of determining the formula and constitution of thevetin was solved in a series of brilliantly executed experiments by Tschesche, *Ber.*, **69,** 2368 (1936). The thoroughly dried glycoside is a hemihydrate of the composition $C_{42}H_{66}O_{18}\cdot 1/2H_2O$, dec. 195°, and a trihydrate is formed on exposure to the air. The genin of thevetin occurs in combination with two molecules of glucose, present in the form of a gentiobiose unit, and one molecule of a methyl ether sugar which probably is digitalose. This sugar has not been identified positively, but it is known to contain one methoxyl group and to be very resistant to hydrolysis. The aglycone thevetigenin ($C_{23}H_{34}O_4$) is known only as the monoanhydro compound, m.p. 218-220°, but the structure is fully established. Thevetigenin is a β,γ-unsaturated lactone (Legal test) having hydroxyl groups at the 3- and 14-positions. That the hydroxyl group at C_{14} is uncombined is shown by the formation of isothevetin, and consequently the entire glycosidic residue is attached at C_3. The aglycone is an epimer of digitoxigenin (IV, p. 276), from which it differs only in the steric arrangement of the C_3-

hydroxyl group. Thevetigenin is a 3(β)-hydroxy compound of the type of cholesterol, while digitoxigenin is a 3(α)-compound (*epi*).

In establishing these interesting facts, Tschesche observed that the two glucose residues can be eliminated easily by hydrolysis with acids, and that on treatment with acetic anhydride and zinc chloride the glycoside can be cleaved partially to give octaacetylgentiobiose. The methyl ether sugar is so firmly bound that its elimination invariably is accompanied by secondary changes. By the action of aqueous alcoholic hydrochloric acid on thevetin at the boiling point the two glucose units were removed, but the tertiary hydroxyl group at C_{14} also was eliminated. Partial hydrolysis of the methyl ether sugar occurs on more prolonged treatment, and anhydrothevetigenin was isolated from the mixture in small amounts by precipitation with digitonin. In order to obtain sufficient material for investigation, Tschesche hydrogenated the crude product of partial hydrolysis and submitted the more stable tetrahydro product to drastic hydrolysis in order to eliminate the methyl ether sugar completely. The tetrahydroanhydrothevetigenin so obtained was not identical with the corresponding saturated hydroxylactone from digitoxigenin, but it yielded on oxidation a ketone identical with tetrahydroanhydrodigitoxigenone.

It is now possible to evaluate the importance of stereochemical factors in determining the cardiac activity of typical heart poisons, whereas previously an interpretation of the differences noted was purely speculative (pp. 285, 300-301). Except for the nature of the sugar residue, which probably is of only minor significance in determining the solubilities, digitoxin, thevetin, and uzarin differ only in the steric arrangement at C_3 and C_5 in the aglycone moiety. The results of K. K. Chen, A. L. Chen and R. C. Anderson,[83] *J. Am. Pharm. Assoc.*, **25**, 579 (1936), reveal considerable differences in the cardiotonic activities, as indicated in the table. Digitoxin, the most active compound of the series in both the cat and frog tests, is a coprostane derivative of the 3(α)- or *epi*-type. An inversion at C_3 results in only a moderate decrease in activity while an inversion at C_5 as well as at C_3 is attended by an enormous drop in the cardiotonic potency. It is evident that allomerization is of considerably greater importance than epimerization in determining the physiological

Minimal Systolic Dosage

	Configuration		Cat unit, mg. per kg.	Frog dose, mg. per g.
	C_3	C_5,A/B		
Digitoxin	α	cis	0.33	0.0080
Thevetin	β	cis	0.92	0.0045
Uzarin	β	trans	5.08	1.5000

properties of both the cardiac drugs and the sex hormones. The previous inference (p. 301) clearly is incorrect.

Convallatoxin (addition to p. 299). The crystalline glycoside convallatoxin (m.p. 238-239°), first isolated by Karrer, *Helv. Chim. Acta*, **12**, 506 (1929), from the blossoms of lily of the valley (*Convallaria majalis*), is of particular interest because of its unusually high activity. The substance surpasses all other known heart poisons in this respect. Tschesche and Haupt, *Ber.*, **69**, 459 (1936), established for convallatoxin the formula $C_{29}H_{42}O_{10}$ by analyses and by determination of the equivalent weight by titration, and characterized the sugar component in the form of an osazone, very probably that of *l*-rhamnose. As the glycoside gives the Legal test and is isomerized by alkali, it evidently contains the usual β,γ-unsaturated lactone ring and C_{14}-hydroxyl group. In addition to the double bond in the lactone ring, convallatoxigenin apparently contains another unsaturated linkage which is very resistant to hydrogenation. The glycoside is hydrolyzed only with difficulty and convallatoxigenin ($C_{23}H_{32}O_6$) itself was not isolated. After benzoylating the crude product of hydrolysis, Tschesche and Haupt succeeded in isolating monoanhydroconvallatoxigenin as the monobenzoate, m.p. 279-281°. They suggest that the benzoyl group probably replaces the original residue attached to a secondary hydroxyl group at C_3. In the Zerwitinoff test two moles of gas were liberated. Tschesche and Haupt considered this to be an indication of the presence of two free tertiary hydroxyl groups, for in a parallel test with anhydrouzarigenin benzoate they observed no evolution of methane resulting from interaction with the lactone ring. From the character of the hydrogenation curve it was concluded that the anhydro linkage and the double bond of the lactone ring absorb hydrogen readily, but that an unreactive nuclear double bond is still present. This does not appear to be conjugated with the anhydro linkage, for the benzoate shows no selective ultraviolet absorption.

Assuming the skeletal structure to be the same as in the other C_{23}-cardiac aglycones, Tschesche and Haupt suggested tentatively that convallatoxigenin has a structure similar to that of periplogenin (II, p. 275) but with an additional tertiary hydroxyl group at C_8 and a double bond at the 9,11-position. This location of the double bond probably would account for its inert character (see p. 411) and for the lack of conjugation with the anhydro linkage, for the latter probably is at C_{14}-C_{15}. A hydroxyl group at C_5 would not be under the activating influence of either double bond of the anhydro compound and might well survive the hydrolysis reaction. Tschesche and Haupt expressed the opinion that a tertiary group at C_8 also would persist during the treatment with acid, but this view has been questioned by Fieser and Newman, *J. Biol. Chem.*, **114**, 707 (1936), who pointed out that in analogy with other cases (p. 280) one would expect a group at C_8 to be activated by the adjacent double bonds at the 9,11- and 14,15-positions and to be eliminated easily with the establishment of a conjugated linkage at C_7-C_8. These authors suggested that the hydroxyl group in question may be present as a substituent in the angular methyl group at C_{10} and that the primary alcoholic group resists benzoylation because of steric effects. Since Jacobs and Elderfield, *ibid.*, **113**, 611 (1936), recently have shown that in the strophanthidin series the CH_2OH group at C_{10} can be benzoylated without difficulty, this view is equally untenable.

There seems to be no way of accommodating an inert nuclear double bond and two tertiary hydroxyl groups to the usual skeletal structure. It will be noted that the evidence for the presence of two tertiary hydroxyl groups is confined to the observation that the anhydroaglycone benzoate liberates two moles of methane in the Zerewitinoff test, and it is possible that the observation was misinterpreted. If the reaction follows the course more usual for aglycone derivatives (p. 408), one mole of gas comes from interaction of the Grignard reagent with the active hydrogen atom of the unsaturated lactone ring and the second mole indicates the presence of a single free hydroxyl group. The evidence regarding the inert center of unsaturation also is capable of an interpretation different from that given by Tschesche and Haupt. The presence of this linkage is inferred from the analytical data and from a slow and partial hydrogenation observed with the glycoside and the aglycone benzoate after the more active double bonds had been saturated. The results would be the same if the aglycone contained an aldehydic group at C_{10} in place of a nuclear ethylenic linkage, for the aldehydic group of strophanthidin is hydrogenated only with great difficulty (p. 265). It is suggested, therefore, that convallatoxigenin is a compound with a saturated ring system, with an aldehydic group at C_{10}, and with hydroxyl groups at C_3, C_5, and C_{14}. It is equally possible, but less likely in analogy with other cases, that one of the tertiary hydroxyl groups is located at C_9 rather than C_5. The suggested structure is that of strophanthidin, and indeed it seems possible that the two aglycones are identical. Jacobs and Collins, *ibid.*, **59**, 713 (1924), report that anhydrostrophanthidin benzoate melts at 287-289°, a value not far from that of the benzoate isolated by Tschesche and Haupt. If not identical, the substances may be stereoisomers.

K. K. Chen, A. L. Chen and R. C. Anderson, *J. Am. Pharm Assoc.*, **25**, 579 (1936), found for convallatoxin the following minimal systolic dosages: 0.08 mg. per kg. cat; 0.00021 mg. per g. frog. For cymarin, a glycoside of strophanthidin, they found the cat and the frog unit to be 0.13 mg.

per kg. and 0.00060 mg. per g., respectively. Convallatoxin is the more potent substance in both tests, and it will be interesting to learn if this is due to a difference in the aglycone moiety or in the sugar residue. Cymarin contains a 2-desoxy sugar and the glycosidic linkage is susceptible to ready hydrolytic cleavage, while convallatoxin contains a firmly bound hexose unit.

According to W. Voss and G. Vogt, *Ber.*, 69, 2333 (1936), convallatoxin probably is the only glycoside of cardiac activity present in *Convallaria majalis*, but it is accompanied by other glycosidic substances. The crude extract has hemolytic and soap-forming properties probably due to the presence of an imperfectly characterized saponin known as convallarin. From the commercial preparation Convallamarin-Merck, Voss and Vogt isolated in a nearly pure but non-crystalline condition a glycoside to which they gave the name **convallamarin,** $C_{44}H_{70}O_{19}\cdot 3H_2O$. The purification was accomplished by a combination of distribution, adsorption, and fractional precipitation procedures. The material had no more cardiac activity in the frog test than could be accounted for by the presence of a trace of convallatoxin, and very feeble hemolytic properties were attributed to a slight amount of convallarin. Convallamarin does not give the Legal test and is not precipitated by cholesterol; the presence of one double bond was indicated by hydrogenation.

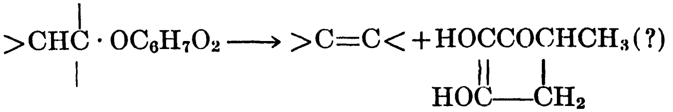
The glycosidic part of convallamarin is composed of two rhamnose and one glucose units and hydrolysis with aqueous acids proceeds no better than in the case of cardiac glycosides which likewise have a hydroxyl or methoxyl group in the sugar unit adjacent to the glycosidic link (rather than CH_2). Under ordinary conditions hydrolysis is only partial and the products are somewhat altered during the drastic treatment required. Voss and Vogt, noting in simple cases that the alcoholysis of a glycosidic linkage proceeds far more readily than hydrolysis, discovered an excellent method of cleavage which should prove of great value in other cases. This consisted in allowing a solution of convallamarin in 2% methyl alcoholic hydrochloric acid to stand for eight days at 35°. The sugar units were eliminated quantitatively as methyl glycosides and the aglycone was isolated in excellent yield in unaltered condition. The aglycone, **convallamaretin,** is assigned the probable formula $C_{26}H_{40}O_5$. It is not a lactone, it contains one double bond, and the Zerewitinoff determination, even at high temperatures, reveals the presence of only two hydroxyl groups.

Antiarins (addition to p. 299). Two isomeric glycosides have been isolated from the gum resin of the upas tree, *Antiaris toxicaria,* a material once used as an arrow poison. One form, now known as α-antiarin, was isolated by Mulder as early as 1838, and the β-isomer (m.p. 225°)

was discovered later by Kiliani. Both varieties of antiarin yield the same ring compound on hydrolysis; they differ in that the β-form yields rhamnose while the α-form yields an isomer of rhamnose. In a reinvestigation of Kiliani's samples, Tschesche and Haupt, *Ber.*, **69,** 1377 (1936), found by analysis and lactone titration that the antiarins have the composition $C_{29}H_{42}O_{11}$. The aglycone resulting from the hydrolysis of the glycosides was characterized as dianhydroantiarigenin, $C_{23}H_{28}O_5$, m.p. 165-167°. This substance shows no characteristic absorption in the region 230-280 mμ, and consequently the anhydro linkages are not conjugated with one another or with a carbonyl group which Kiliani had recognized as present in the glycosides and in the aglycone. Although β-antiarin does not respond to sensitive tests for aldehydes, Tschesche and Haupt note that the same is true of strophanthidin. As the dianhydro compound contains only one secondary hydroxyl group, these investigators call attention to the possibility that antiarigenin, $C_{23}H_{32}O_7$, may differ from strophanthidin only in the presence of an additional tertiary hydroxyl group (probably at C_9).

K. K. Chen, A. L. Chen and R. C. Anderson (*loc. cit.*, p. 417, private communication from Dr. K. K. Chen) report the following activities for the two glycosides: α-antiarin, 0.13 mg. (cat unit), 0.00050 mg. (frog dose); β-antiarin, 0.10 mg. (cat unit), 0.00039 mg. (frog dose). The somewhat greater activity of β-antiarin in both tests shows that the nature of the sugar moiety is of definite, if minor, significance.

Calotropin (addition to p. 299). Hesse and Reicheneder, *Ann.*, **526,** 252 (1936), established for this African arrow poison the probable formula $C_{29}H_{40}O_9$. On being heated at 230° in high vacuum, the substance is cleaved into calotropagenin ($C_{23}H_{32}O_6$), an isomer of strophanthidin, and a methylreductinic acid, probably as follows:



$$>\mathrm{CH}\underset{|}{\overset{|}{\mathrm{C}}}\cdot \mathrm{OC_6H_7O_2} \longrightarrow\ >\mathrm{C{=}C}< + \mathrm{HOC}\underset{\mathrm{HO}\overset{\|}{\mathrm{C}}\text{——}}{\mathrm{C}}\mathrm{O}\underset{\overset{|}{\mathrm{C}}\mathrm{H_2}}{\mathrm{C}}\mathrm{HCH_3}(?)$$

The methylreductinic acid, which in the free state has powerful reducing properties, probably is linked to the genin through one of the enolic hydroxyl groups, as calotropin is stable in the air.

Basic Constituents of the Secretions (p. 303). In a further investigation, Jensen and K. K. Chen, *J. Biol. Chem.*, **116,** 87 (1936), found that the "bufotenines" of different origins[93] are identical with the bufotenine investigated by Wieland and co-workers.

Bufotalin (pp. 306-311). In a further investigation of this genin and its companion substances, Wieland, Hesse and Hüttel, *Ann.*, **524,** 203 (1936), developed a simpler and improved method of isolation based upon the use of chromatographic adsorption. The material was extracted with chloroform from the dried secretion, de-fatted with petroleum ether, and adsorbed on alumina from an acetone solution, a yellow impurity serving as an indicator for bufotalin. After developing the chromatogram with chloroform, bufotalin and a mixture of companion substances were found in different zones and a fairly sharp separation was possible. From 33,000 toads there was obtained 36 g. of bufotalin and about 29 g. of companion poisons, or about 2 mg. of active material per toad.

It was found that bufotalin has the same type of absorption spectrum as scillaridin A (p. 299), the maximum in each case being at 300 mμ. Since there is a considerable body of evidence indicating that the absorbing group of scillaridin A is a doubly unsaturated lactone ring, it seemed likely that the same group is present in bufotalin. This inference was strengthened by the observation that the genin was not attacked by perbenzoic acid and that on ozonization of acetyl bufotalin a substance giving a color test for glyoxylic acid was formed, and consequently Wieland is inclined to believe that both of the double linkages of bufotalin are located in the lactone ring and that the nucleus is saturated. This view would necessitate the rejection of the previous conception of the relationship between bufotalin and bufotoxin (pp. 304-305), and, if the suberylarginine residue is eliminated by a process of true hydrolysis, it would have to be supposed that bufotoxin contains one molecule of water of crystallization not eliminated in drying: $C_{26}H_{35}O_5 \cdot OCOR \cdot H_2O$, rather than $C_{26}H_{37}O_6 \cdot OCOR$. Wieland favors this view and suggests that the suberylarginine residue is attached to the tertiary hydroxyl at C_{14}. A further difficulty is encountered in attempting to account for the relationship of bufotalien to bufotalin and to bufotoxin (p. 310). Since the two additional nuclear double linkages of bufotalien produce no noticeable effect on the absorption spectrum, Wieland thinks it is unlikely that they are conjugated with one another, but if this is the case it is difficult to see why they invariably appear concurrently in the dehydration reactions. The acetoxyl group which is susceptible to ready elimination along with the tertiary hydroxyl at C_{14} can hardly be present in secondary combination if an activating double bond actually is absent, and Wieland considers that it must be located at C_5 or C_9. In either case the dianhydro compound might contain unconjugated double bonds, but it is odd that there should be no differentiation in the ease with which they are introduced. It is evident that there are inconsistencies in the interpretation suggested on the basis of the absorption spectra. Bufotoxin itself has the same type of absorption spectrum as bufotalin and bufotalien, and it is perhaps significant that the relationship between the conjugated compound and the dianhydro genin of the series is exactly the same as that between scillaren A and scillaridin A (p. 299). In the latter case it seems very odd that both compounds exhibit similar absorption maxima, for there are definite indications that the dianhydro compound contains a conjugated system of double bonds in the nucleus (p. 298) and yet there is no evidence of selective absorption at 240 mμ or at 280 mμ, as would be expected if conjugated double bonds were present in different rings, or in the same ring, respectively. Both problems probably are related, and both remain obscure.

In the course of their work, Wieland, Hesse and Hüttel made a further characterization of two companion substances observed in the earlier investigation of Wieland and Hesse.[1] These substances are acetyl-free and may be related to the hypothetical genin $C_{24}H_{34}O_5$ of which bufotalin is the acetyl derivative. **Bufotalidin,** $C_{24}H_{32}O_6$, m.p. 228°, contains one more double bond and one more hydroxyl group than bufotalin. The lactone ring is opened by methyl alcoholic potassium hydroxide and there is formed an oxidic ester exactly analogous to isoscillaridinic acid methyl ester (VIII, p. 297). Coupled with the fact that the genin shows an absorption maximum of 300 mμ, this observation clearly points to the presence of the doubly unsaturated lactone ring characteristic of scillaridin A. **Bufotalinin,** $C_{24}H_{30}O_6$, also shows an absorption maximum at 300 mμ. In the Zerewitinoff test for active hydrogen, two moles of gas were liberated at 28° and a further mole was evolved at 95°, suggesting the presence of two secondary and one tertiary hydroxyl groups. Treatment with methyl alcoholic potassium hydroxide gave a yellow salt of a stable enol ester. That an oxidic ester is not formed may mean that the usual C_{14}-hydroxyl group is absent or that the steric arrangement does not permit cyclization.

Other Genins (pp. 311-316). Wieland, Hesse and Hüttel (*loc. cit.*) found that the absorption spectra of gamabufogenin and arenobufagin are similar to those of scillaridin A and bufotalin, showing maxima in the region 300 mμ. This is a preliminary indication of the presence in these toad poisons of the type of lactone ring characteristic of scillaridin A.

Cinobufagin (p. 312). X-ray crystallographic determinations of the molecular weights of cinobufagin, its acetyl derivative, and of cinobufagone have confirmed the previous indications that cinobufagin has the formula $C_{26}H_{34}O_6$ [Crowfoot and Jensen, *J. Am. Chem. Soc.*, **58,** 2018 (1936)]. Tschesche and Offe, *Ber.*, **69,** 2361 (1936), found that the absorption spectrum is similar to those of scillaridin A and bufotalin (p. 420), having a maximum at about 290 mμ. On ozonization of the genin they detected the formation of formic acid, and the presence of a free or latent aldehydic group was established in the product of careful hydrolysis. These observations strongly suggest the presence of the doubly unsaturated lactone ring characteristic of scillaridin A. As Tschesche and Offe observed the formation of a hexahydro compound (two forms) on hydrogenation, while Jensen[7] obtained a tetrahydro derivative, it is probable that the genin has one nuclear double bond which is somewhat inert, in addition to two double linkages in the lactone ring. On saponification of the hexahydro compounds, the acids formed promptly undergo dehydration without loss of the acidic character, and from this Tschesche and Offe inferred that the genin has a tertiary hydroxyl group at the 14-position which enters into the formation of an oxide ring. There are as yet no indications concerning the location of the secondary hydroxyl group, the nuclear double bond, and the acetoxyl group.

Bufagin (pp. 314-315). Tschesche and Offe, *Ber.*, 69, 2361 (1936), found that bufagin ("marinobufagin") has an absorption maximum at 300 mμ and absorbs three moles of hydrogen on catalytic hydrogenation. Two of the double bonds probably are located in the lactone ring and, since Jensen and Evans[14] obtained a tetrahydro derivative, the third double bond seems to be fairly inert and may be situated in the nucleus (possibly at C_9-C_{11}). Jensen (private communication) has suggested that the group at C_{10} is CH_2OH rather than CHO, as proposed in the first edition, and if this is the case the genin probably contains two tertiary hydroxyl groups (possibly at C_5 and C_{14}).

Chapter VII

Triterpenoid Sapogenins (pp. 318-321). The investigation of the structures of compounds of this group continues to attract considerable interest, but the problem is not yet solved and the views of prominent workers in the field are still speculative and provisional. Ruzicka has abandoned the skeletal structure previously attributed to ring A of the triterpenoid compounds (I, p. 320) on the basis of dehydrogenation experiments [Ruzicka, K. Hofmann and Frei, *Helv. Chim. Acta,* 19, 386 (1936)]. The trimethylnaphthol isolated in some of the experiments was believed to be a 1,2,7-trimethylnaphthol because it yielded a hydrocarbon at first regarded as sapotalene on treatment with zinc dust at 400°, but the substance was not identical with any of the five possible hydroxyl derivatives of sapotalene, all of which were synthesized for comparison [Ruzicka, Hösli and K. Hofmann, *ibid.*, 19, 370 (1936)]. Suspecting that a rearrangement occurs in the zinc dust distillation, and in order to avoid this complication, the trimethylnaphthol was converted into a perhydrogenated hydrocarbon and this was dehydrogenated. The product was at first believed to be 1,2,8-trimethylnaphthalene, but in later work it was identified as 1,2,5-trimethylnaphthalene [Ruzicka, K. Hofmann and Schellenberger, *ibid.*, **19**, 1391 (1936)]. The hydroxy compound obtained by dehydrogenation was found to be identical with synthetic 1,2,5-trimethyl-6-naphthol. To account for the formation of this substance, Ruzicka altered his proposed formula, for example for oleanolic acid (IV, p. 321), by retaining the hydroxyl group at position 2, transposing the *gem.*-dimethyl group to 1, and moving the angular methyl group to the bridge head adjacent to position 4.

Further experiments on the degradation of oleanolic acid and sumaresinolic acid have led Ruzicka to alter also the formulation of ring E [Ruzicka, Hösli and K. Hofmann, *ibid.*, **19**, 109 (1936); Ruzicka and K. Hofmann, *ibid.*, **19**, 114 (1936)]. The carboxyl group is transposed to the alternate bridge head and the double bond is moved to the adjacent γ,δ-position in the ring. The properties of betulin can be interpreted satisfactorily on this basis [Ruzicka and Isler, *ibid.*, **19**, 506 (1936)]. Gypsogenin has been related to the most extensively characterized compounds of the group. Ruzicka and Giacomello, *ibid.*, **19**, 1136 (1936), converted this substance into oleanolic acid on reduction of the carbonyl group by the Wolff-Kishner method.

In an attempt to identify the picene homologue obtained as a dehydrogenation product, Ruzicka and Mörgeli, *ibid.*, **19**, 377 (1936), synthesized the 3,8-dimethyl and the 3,9,10-trimethyl derivatives of picene, but neither substance was identical with the degradation product. Drake and Duvall, *J. Am. Chem. Soc.*, **58**, 1687 (1936), obtained sapotalene, 2,7-dimethylnaphthalene, and a picene homologue from ursolic acid by selenium dehydrogenation.

From his studies of the degradation of oleanolic acid and hederagenin, Kitasato, *Acta Phytochim.* (*Japan*), **9**, 43, 61, 75 (1936), has arrived at a provisional conception of the structures which is somewhat different from his earlier formulation (V, p. 321) but very similar to that most recently suggested by Ruzicka. His formulation of ring E coincides with that of Ruzicka except that the double bond is placed at the alternate γ,δ-position; in ring A the hydroxyl and *gem.*-dimethyl groups are assigned the positions 2 and 1, respectively, as above. A hydroxyl group in this position of the phenanthrene ring system (ABC) would correspond to the characteristic C_3-hydroxyl group of the sterols. According to Askew, *J. Chem. Soc.*, 1585 (1936), the results of surface film measurements are in accord with this formulation [see also Spring, *Chemistry and Industry*, **55**, 964, 1050 (1936)].

Other work on the triterpenoid sapogenins is reported in the following papers: Ruhkopf and Mohs, *Ber.*, 69, 1522 (1936); Grasshof and Wedekind, *ibid.*, 69, 2686 (1936); Sone, *Acta Phytochim.* (*Japan*), 9, 83 (1936); Kuwada, *J. Pharm. Soc. Japan*, 55, 1258 (1935); 56, 469 (1936); Fujii and Matsukawa, *ibid.*, 55, 1322 (1935); 56, 408 (1936); Nozoe and Katsura, *J. Chem. Soc. Japan*, 57, 692 (1936); Ruzicka and Leuenberger, *Helv. Chim. Acta*, 19, 1402 (1936).

The substances **friedelin** and **cerin,** which can be extracted from cork with ethyl acetate, have been recognized as triterpenoid compounds by Drake and co-workers (Jacobsen, Shrader, Campbell, Haskins), *J. Am. Chem. Soc.*, 57, 1570, 1854 (1935); 58, 1681, 1684 (1936). Friedelin ($C_{30}H_{50}O$) is a ketone, cerin ($C_{30}H_{50}O_2$) is a hydroxyketone, and both compounds can be converted into the same hydrocarbon. The triterpenoid character was established by the observation that the alcohol from friedelin on dehydrogenation with selenium yields sapotalene, 1,2,8-trimethylphenanthrene, and a picene homologue. By oxidative degradation it was found that friedelin contains the group $—CH_2COCH<$.

Another compound apparently related to oleanolic acid and hederagenin is **quinovic acid,** which has been studied by Wieland and coworkers (Erlenbach, Hoshino, Utzino, K. Kraus, A. Hartmann, Dietrich), *Ann.*, 453, 83 (1927); 479, 179 (1930); 488, 242 (1931); 497, 140 (1932); 522, 191 (1936). The compound is obtained by the hydrolysis of the glycoside quinovin, found in cinchona bark. Quinovic acid is a hydroxy dibasic acid, $C_{30}H_{46}O_5$. It loses carbon dioxide readily when heated and yields pyroquinovic acid. Dehydrogenation with selenium affords in unusually good yield a hydrocarbon ($C_{25}H_{20}$) which was characterized as a picene homologue by examination of the absorption spectrum. In addition to this evidence, the chemical properties of the compound indicate a relationship to the triterpenoid sapogenins.

Other additions to the large group of substances now classified as triterpenoid in character are the alcohols **lanosterol** and **onocerin** (p. 358, which previously were regarded as sterols.

New Saponins and Sapogenins (pp. 321-324). Tschesche, *Ber.*, 69, 1665 (1936), isolated **tigonin** in a pure condition from *D. lanata* by precipitating the substance as the sparingly soluble and nicely crystalline molecular compound with cholesterol. Tigonin was recovered from purified cholesterol tigonide by dissociation with pyridine and precipitation with ether. The addition compound contains one molecule of each component. As the solubility in alcohol (0.15 g. in 100 cc. of 95% alcohol at 18°) is considerably greater than that of cholesterol digitonide (0.014 g.), tigonin is less suitable than digitonin for use as a precipitant. Tschesche noted that, since the sugar residue of tigonin can be linked to the aglycone nucleus only at the C_3-hydroxyl group, this probably represents the point of attachment of the glycoside units of the other saponins. The plant heart poisons are now recognized as being similarly constituted in this respect.

From the California soap plant *Chlorogalum pomeridianum,* Jurs and Noller, *J. Am. Chem. Soc.,* **58,** 1251 (1936), isolated a crystalline saponin to which they assigned the name **amolonin** (see table, p. 324). The aglycone obtained on hydrolysis is identical with that from tigonin. **Smilagenin,** a substance which appears to be an isomer of sarsasapogenin and which is more soluble than this substance, was isolated from Jamaican sarsaparilla root (*Smilax ornata*) by Askew, Farmer and Kon, *J. Chem. Soc.,* 1399 (1936). Smilagenin is precipitated slowly by digitonin and yields a desoxy compound different from desoxysarsasapogenin.

Structure of Digitogenin and Gitogenin (pp. 323-336). At the time of the publication of the first edition it was not known with certainty whether the hydroxyl groups in ring A of digitogenin and gitogenin are situated at the 2- and 3-positions or at positions 3 and 4. The evidence from the early literature on this point was in some respects definitely contradictory, as certain of the observations indicated the 2,3-structure while other data were reconcilable only with the alternate formulation (pp. 325-327, 335-336). The most important arguments in favor of placing the hydroxyl groups at the 3- and 4-positions centered around the composition and properties of the "acid A" of Windaus and Willerding (pp. 326, 334). While the alternate formulation afforded a much more reasonable interpretation of many of the reactions of the genins, it seemed to be definitely excluded on the basis of the properties attributed to acid A by Windaus and Willerding. Recognizing the importance of evaluating this evidence, Tschesche and Hagedorn, *Ber.,* **69,** 797 (1936), reinvestigated the acid and its derivatives. They found the early work to be seriously in error. Acid A is not $C_{26}H_{38}O_{12}$, as it was at first supposed, or $C_{27}H_{40}O_{12}$, according to the revised formulas of the genins, but $C_{23}H_{32}O_{10}.H_2O$. The acid is tetrabasic and not pentabasic and it is not a compound of the malonic acid type but a β-keto acid. The early analyses of the decarboxylation product, "acid B," and of its ester also were found to be erroneous. Acid B is a tribasic acid of the composition $C_{22}H_{32}O_8.H_2O$, and the ester does not liberate methane in the Zerewitinoff test. All of the arguments based upon the previous reports clearly fall into the discard, and the balance of evidence now indicates almost beyond question that the hydroxyl groups in the terminal ring of digitogenin and gitogenin are located at C_2 and C_3.

On the basis of the revised formulas for acids A and B and the new evidence concerning the nature of these substances, Tschesche and Hagedorn suggested formulations consistent with the 2,3-structure which provide an entirely rational account of the observations. The inconsistencies in the alternate interpretation of other relationships also vanish. Digitogenic acid no longer need be regarded as a β-keto acid of unique properties, but can be assigned the more rational formula of a γ-keto acid (V, p. 326). The formation of an enol lactone from the trimethyl ester of oxodigitogenic acid (p. 335) becomes understandable, and the opening of ring A in the oxidation (p. 336) follows the course expected in analogy with other cases. The only observation with which the revised formulas do not appear to be in harmony is the difference in the velocity of hydrolysis of the two ester groups of gitogenic ester noted by Jacobs and Simpson[27] (p. 327). It seems necessary to conclude that such evidence does not provide a reliable guide in the determination of structure.

Since acids A and B do not have the formulas or the properties originally attributed to them, the reasoning leading to the proposal of an ethylene oxide structure for the sapogenin side chain (p. 334) is no longer valid. The suggestion, however, still merits consideration and further evidence will be required in order to distinguish between the alternate formulations for the terminal part of the side chain.

Determination of Empirical Formulas by Analysis (addition to p. 325). Frequent reference has been made to the difficulty in determining the formulas of natural products by direct analysis (pp. 133, 291, 295, 325), and to the difficulties often encountered in the combustion of phenanthrene derivatives (pp. 54, 206, 225). Ordinary carbon-hydrogen determinations are not sufficiently precise to distinguish between homologues of molecular weights of the order of 350-450, where the differences in the composition for alternate formulas is no more than 0.06-0.5% carbon and 0.09-0.2% hydrogen, depending upon the amount of oxygen present in the compound. In some cases it is possible to analyze derivatives having higher percentages of oxygen, halogen, or nitrogen than the parent substance, for this may increase the spread in the carbon values for alternate formulas differing by CH_2 to as much as 0.4-0.6%, although the hydrogen values are but little affected. Reinitzer, *Monatsh.*, 9, 421 (1888), characterized cholesterol by the analysis of the acetate dibromide, Windaus, v. Werder and Gschaider, *Ber.*, 65, 1006 (1932), made use of sterol bromoacetates and nitrobenzoates, and Drake and Jacobsen, *J. Am. Chem. Soc.*, 57, 1570 (1935), employed *p*-iodobenzoyl derivatives.

Naturally occurring acids and lactones often can be characterized satisfactorily by a careful determination of the neutralization equivalent [Windaus and Brunken, *Z. physiol. Chem.*, 140, 48 (1924); Stoll, A. Hofmann and Peyer, *Helv. Chim. Acta*, 18, 1247 (1935)]. In the case of an alcohol, a determination can be made of the saponification equivalent of the acetate or benzoate [Vesterberg, *Ark. Kemi, Minerol. Geol.*, **9**, No. 27, 1 (1926); Sandqvist and Gorton, *Ber.*, **63**, 1935 (1930); **64**, 2167 (1931); Windaus, v. Werder and Gschaider, *loc. cit.*]. Drake and Jacobsen (*loc. cit.*) determined the saponification equivalents of a series of homologous esters. In any of the methods depending upon acidimetry, it usually is necessary to employ a rather large sample (0.5-1 g.) in order to determine the molecular weight with an accuracy of 2-3 units (Stoll, Sandqvist).

The X-ray and crystallographic method also is of distinct value in the determination of molecular weights in those cases where it is applicable (pp. 308, 312, 314, 421). All these methods have been found useful, and yet they all are subject to some limitations.

Recently Fieser and Jacobsen, *J. Am. Chem. Soc.*, **58**, 943 (1936), applied to the problem the technique of precision combustion developed by Baxter and Hale, *ibid.*, **58**, 510 (1936), in an investigation of the atomic weight of carbon. The combustion is conducted at a rather high temperature in a quartz tube with a filling of platinum catalyst and a fairly short layer of copper oxide. Typical results obtained in individual analyses with samples weighing about 1 g. are as follows (calculated for C = 12.01).

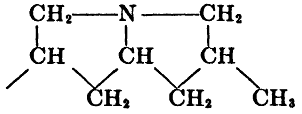
	% C		% H	
	Found	Calcd.	Found	Calcd.
Triphenylbenzene ($C_{24}H_{18}$)	94.074	94.079	5.918	5.921
Dihydrocholesterol ($C_{27}H_{48}O$)	83.439	83.436	12.433	12.447
Chlorogenin ($C_{27}H_{44}O_4$)	74.961	74.956	10.250	10.250
Sarsasapogenin ($C_{27}H_{44}O_3$)	77.827	77.835	10.644	10.644
Fichtelite ($C_{19}H_{34}$)	(86 875)	86.945	13.062	13.056

In general the results agreed with the theoretical values within 0.02% for carbon and 0.01% for hydrogen, and it is evident that in at least some cases substances of both plant and animal origin can be prepared in a very high state of purity. The percentages found for sarsasapogenin fully confirm the C_{27}-formula. The precision analysis of chlorogenin led to a revision of the formula $C_{26}H_{42}O_4$ previously attributed[23] to the sapogenin on the basis of numerous macro- and micro-analyses of the compound and its derivatives, of saponification equivalents, and of molecular weight determinations.

Sarsasapogenin (p. 336). From surface film measurements Askew, Farmer and Kon, *J. Chem. Soc.*, 1399 (1936), found for tigogenin, gitogenin, and sarsasapogenin the limiting areas 38, 39.5, and 42 sq. Å per molecule, respectively. The accepted formulas for the first two compounds are entirely consistent with the areas found. The value for sarsasapogenin, however, cannot be reconciled with a formula in which the water-attracting hydroxyl group is at C_{11}, as suggested by Simpson and Jacobs, rather than at the end of the molecule. From an examination of models the English investigators conclude that the hydroxyl group can only be accommodated at C_2, C_3 or C_4. They note that the 4-position is unlikely because sarsasapogenin (but not its epimer) is precipitated by digitonin, in contrast to 4-cholestanol and its epimeric form. The fact that sarsasapogenone is not isomerized by fairly vigorous treatment with alkali also indicates that the carbonyl group probably is not at the α-position 4, although by analogy with the α-decalones this argument may be valid only in the cis (coprostane) series.

From the fragmentary information at present available, it appears likely that sarsasapogenin is a coprostane derivative hydroxylated in the usual sterol position (C_3), that is, that it has the same structure as tigogenin but differs in the manner in which rings A and B are joined. The dibasic lactone acid III would then have the formula II, p. 332 (erroneously attributed in the first edition to the oxidation product of gitogenic acid), while the lactone VII would be assigned the structure of V, p. 331, and the configuration of a coprostane, rather than a cholestane, derivative. (According to a preliminary report [*Chemistry and Industry*, **55,** 925 (1936)] which has become available since the above was written, Kon and Farmer have degraded sarsasapogenin to aetiobilianic acid. This result proves that the sapogenin belongs to the coprostane series and that one of the oxide rings is linked to C_{16}).

Alkaloids Related to the Sapogenins (addition to p. 337). There are indications that certain alkaloids and alkaloidal aglycones contain the reduced cyclopentenophenanthrene ring system and are in fact closely related in structure to the steroid sapogenins. The eyes or shoots of potatoes contain the glycoalkaloid **solanine,** together with the corresponding aglycone, **solanidine.** The formula established for solanidine, $C_{27}H_{43}ON$, is suggestive of a relationship to the sapogenins of the digitalis group or to cholesterol, and like the latter compound solanidine contains one double bond and is precipitated by digitonin. Soltys and Wallenfels, *Ber.*, **69,** 811 (1936), defined these relationships more clearly than in the earlier literature and, in order to extend the evidence, they submitted to dehydrogenation with selenium the anhydro derivative of solanidine, known as solanthrene or solanidiene. From the reaction mixture they isolated a substance which was fully identified as the Diels hydrocarbon. In analogy with the many known cases, this establishes the nature of four of the six rings indicated by the analysis and properties. Soltys and Wallenfels noted that the precipitability with digitonin affords some indication that the hydroxyl group is located in the 3-position, and they suggested that the double bond may occupy a position corresponding to that of cholesterol. Clemo, W. M. Morgan and Raper, *J. Chem. Soc.*, 1299 (1936), suggested a plausible if entirely provisional formulation which incorporates the nitrogen atom into the cholesterol side chain. Their formula represents solanidine as differing from cholesterol only in having the side chain:



From the leaves of the South African winter cherry, *Solanum pseudocapsicum*, Barger and Fraenkel-Conrat, *ibid.*, 1537 (1936), isolated the alkaloids **solanocapsine** and **solanocapsidine.** The provisional formulas are $C_{26}H_{44}O_2N_2$ and $C_{26}H_{42}O_4N_2$, respectively. The second of these substances on dehydrogenation with selenium yielded the Diels hydrocarbon.

AUTHOR INDEX

Abderhalden, 115, 134
Abel, G., 130
Abel, J. J., 302
Achtermann, 174, 373
Adam, 149, 196, 206
Adams, R., 110
Adelson, 343, 344
Adkins, 14
Adler, 244
Ador, 100
Aherns, 344
Albert, 9
Albrieux, 405
Alder, 2
Allen, E., 191, 192, 240
Allen, W. M., 196, 241, 242, 244, 245, 402
Alles, 304
Anchel, 384, 405
Anderson, R. C., 299, 411, 415, 417
Anderson, R. J., 112, 113, 118, 365
Andervont, 87
Ando, 403
Angelescu, 358
Angus, 179
Ankersmit, 60
Anschütz, 14, 15, 195
Apfelbaum, 78
Arbusow, 60, 63
Arnaud, 290, 291
Aschan, 51
Aschheim, 192, 199
Askew, 179, 423, 425, 427
Auhagen, 373
Aumüller, 320
Auwers, v., 173, 220
Avenarius, H., 32
Avenarius, R., 105
Ayling, 340

Bachmann, 5, 9, 10, 11, 340, 342, 354, 370
Bacon, 345
Bagley, 50
Balas, 50, 52, 53, 70
Balint, 190
Balle, 30
Bamberger, 54, 70
Bandte, 259, 276
Bang, 119
Bann, 381
Barbour, 344
Bardhan, 13, 76, 220, 387, 388
Barger, 42, 429
Barnett, 109
Barr, 381, 393
Barry, 88, 91, 162
Bauer, 15
Bauman, 125, 368
Baup, 53
Baxter, 427
Beall, 197, 205, 383
Behr, 100, 143
Behrend, 12
Behring, v., 113, 122
Benedict, 126
Bengtsson, 357
Berenblum, 92
Berg, 405
Berger, F., 42
Berger, H., 357
Bergmann, E., 79, 94, 163, 166, 370, 371
Bergmann, F., 72, 94, 371
Bergmann, W., 121, 128, 174
Bergs, 13
Bergsteinson, 319
Berliner, 370
Bernal, 148, 150, 164, 206, 227, 384
Bernette, 51
Bertrand, 303
Beschke, 21
Beynon, 340, 364
Bigelow, 259, 261, 284, 291, 294
Bills, 120, 181, 378
Bistrzycki, 62
Blanc, 140
Blanke, 243
Bloch, 82
Blum-Bergmann, 72, 79, 370
Boatner, 340, 342
Boedecker, 132
Boersch, 127
Bogert, 13, 68, 79, 343, 344, 348
Bohle, 284, 409, 410, 413
Bohne, 126, 127, 289, 299
Bondi, 125
Bonstedt, 176
Borchardt, 194
Borek, 384
Borgeaud, 176
Borsche, 137, 138, 143
Bossert, 152
Bosshard, 403
Bottomley, 91
Bougault, 220
Bourdillon, 179
Bouveault, 341
Boyland, 353
Brady, 382
Branch, 92, 352

Brandenberger, 158, 167
Brass, 6
Braun, v., 20, 21
Bredig, 11
Breusch, 122
Brigl, 126
Brockmann, 378, 379
Brody, 299
Bromeis, 69
Brovsin, 396
Browning, 92, 352
Bruce, 179
Brues, 353
Brüngger, 115, 226, 230, 319
Brunken, 173, 426
Bryant, 255
Bucher, 56
Buchholz, 374
Buckow, 28
Buño, 405
Burchard, 117
Burger, 9, 11, 14, 47, 343, 344
Burr, 112
Burrows, 87, 218, 352, 386
Burström, 200
Busse, 181
Bussemaker, 259
Butenandt, 119, 168, 191, 193, 194, 195, 199, 200, 201, 203, 206, 207, 208, 221, 224, 225, 229, 232, 234, 235, 236, 238, 240, 241, 242, 243, 244, 246, 248, 249, 250, 251, 359, 393, 395, 397, 402, 403

Callow, 179, 237, 299, 359, 368, 373, 394
Campbell, 424
Carminati, 405
Cartland, 195, 202
Chakravorty, 170, 229, 233
Chargaff, 130
Chatterjee, 223, 356
Chen, A. L., 299, 300, 302, 303, 312, 316, 411, 415, 417
Chen, K. K., 299, 300, 302, 303, 312, 314, 316, 411, 415, 417, 419
Chen, Y. H., 379
Chevallier, 382
Cholnoky, v., 374
Chouard, 199, 384
Chuang, 170, 233, 289, 389, 391
Cioranescu, 370
Clapp, 92, 352
Clar, 2, 5, 18, 19, 100, 105, 343
Clark, J. M., 4
Clarke, 384
Clauberg, 241
Claus, 100
Clemo, 159, 162, 429
Cloetta, 259, 278, 299
Cobler, 229, 246, 395
Coffey, 122, 365
Cohen, A., 162, 166, 209, 211, 223, 388
Cohen, F. L., 5, 343
Cohen, J. B., 92
Cohen, S. L., 194, 201, 382
Collins, 263, 266, 270, 417
Cook, J. W., 9, 13, 16, 17, 22, 83, 86, 88, 91, 93, 94, 97, 98, 99, 101, 102, 104, 108, 109, 158, 159, 161, 162, 166, 167, 209, 211, 213, 216, 221, 223, 348, 349, 352, 356, 370, 385, 388, 390
Cooper, 92
Corbellini, 88, 405
Cormier, 5
Corner, 241, 244
Cornil, 382
Cortese, 125, 368
Coulson, 102, 108
Cox, 181
Crooks, 362, 397
Crowder, 365
Crowfoot, 164, 308, 384, 389, 421
Curtis, 194, 197, 200
Cushny, 257

Dalmer, 140, 177, 231
Dam, 117, 118, 119, 121
Dane, 85, 132, 133, 139, 148, 150, 153, 154, 155, 156, 168, 382, 403
Danielli,, 196, 206, 208
Dannenbaum, 232, 234
Dannenberg, 397
Dansi, 159. 167
Darzens, 65, 79, 80. 348, 390
David, 195, 202, 213, 215, 234, 237, 238
Davidson, 78, 348
Deanesley, 229, 237, 396, 397
Decker, 22
Dennison, 237, 396
Deppe, 179, 375
Desalbres, 51
Dessau, 394
Deulofeu, 198, 303
Dickenson, 159
Diebold, 364
Diels, 2, 58, 115, 134, 149, 158, 165, 167
Dietrich, 424
Dietz, 100, 369
Dimroth, K., 182, 371, 375
Dingemanse, 193, 194, 218, 237, 238, 396
Dirscherl, 202, 212, 226, 229, 231, 382, 384, 391
Dithmar, 179, 374
Dodds, 196, 216, 385, 386
Doescher, 341
Dohrm, 213
Doisy, 190, 191, 193, 194, 197, 200, 201, 206, 207, 214, 215, 385
Dols, 378
Dorée, 159, 358
Dorfman, 394
Dorp, van, 100
Doubilet, 366
Douglas, 43
Drake, 423, 424, 427
Dreifuss, 82
Drekter, 360

Drummond, 380
Dubourg, 50
Dunn, 173
Dupont, 50, 51
Duvall, 42

Easterfield, 50
Eddy, 46, 344
Edmunds, C. W., 46, 257
Edson, 383
Egli, 319
Ehmann, 160, 220, 319
Eichenberger, 115, 226, 229
Eickel, 30
Eilers, 344
Eisenbrand, J., 42
Eisenbrand, L., 42
Ekstrand, 53
Elbs, 100
Elderfield, 261, 262, 272, 274, 276, 277, 285, 288, 289, 290, 408, 412, 413, 414, 417
Ellingworth, 92
Ender, 177
Engel, 405
English, 30
Erdtmann, 6
Erlenbach, 424
Erxleben, 22, 24
Euler, v., 200
Evans, 282, 314, 359, 361, 398
Everest, A. E., 16
Everse, 406

Fahrion, 61
Faragher, 50
Faris, 343
Farmer, 425, 427, 428
Fehling, 53
Fels, 242, 243, 245, 402
Fernholz, 119, 127, 157, 170, 171, 179, 229, 233, 234, 236, 243, 246, 247, 248, 289, 358, 364, 369
Ferrari, 198
Fevold, 242
Fex, 119
Fieser, L. F., 3, 7, 8, 10, 11, 13, 14, 19, 71, 74, 86, 88, 93, 94, 98, 100, 105, 106, 107, 110, 130, 221, 340, 341, 342, 343, 347, 353, 354, 355, 387, 388, 413, 417, 427
Fieser, M., 93, 98, 110, 340, 343, 355, 388
Fischer, H., 125, 126, 371
Fischer, O., 26
Fischer, W., 240, *see* W. H. Fischer
Fischer, W. H., 396, 403, 404
Fischmann, 179
Fitch, 343
Fittig, 1
Fleck, 164, 287, 322, 324
Fleming, 363
Fonrobert, 50
Fortner, 56
Foster, 344
Fraenkel, 241
Fraenkel-Conrat, 429
Frank, 53, 60, 143
Freese, 259, 279
Frei, 422
Fremery, de, 244, 406
Freud, 218, 234, 237, 238
Frey, 8
Fridenson, 195, 201, 213
Friedlaender, 15
Fries, 2
Fritzsche, 53
Fuchs, 324
Fujii, 393, 395, 397, 403, 424
Funke, 343
Furter, 113, 158, 167, 319
Fussgänger, 236

Gadamer, 39, 41, 42
Gad-Andresen, 191, 200
Gädke, 115, 149, 158
Gaede, 179, 182
Gallagher, 224, 237, 394
Gamble, 165
Gattermann, 125
Gaudefroy, 201
Gay, 344
Gehrke, 234
Gephart, 364
Gessner, 299
Ghatak, 300
Ghose, 42
Giacomello, 423
Girard, 195, 197, 201, 209, 211, 213, 383
Girardet, 42
Gley, 299
Goebel, 199
Goetsch, 402
Goldberg, A., 130, 132
Goldberg, M. W., 53, 60, 158, 160, 167, 220, 226, 229, 230, 233, 234, 235, 240, 363, 396, 401
Goldschmidt, 11
Gorton, 169, 427
Goto, 37, 38, 42, 343
Gottberg, v., 117, 121
Gottfried, 391
Graaff, de, 53, 64
Grab, 379, 380
Graebe, 1, 93
Graff, 123
Grasshof, 115, 424
Grave, 276
Greenwood, 216
Grosse, 393
Gruber, 110
Grundmann, C., 341
Grundmann, W., 377
Gschaider, 169, 426, 427
Guiteras, 167, 171, 182
Gulbransen, 92, 352
Gulland, 24, 35, 42, 43, 44
Gumlich, 126

Gunn, 257
Gustus, 259, 264, 265, 267, 271, 272, 276, 277, 278, 279, 408
Guthrie, 11

Haack, 259, 283
Haar, van der, 324
Haberland, 388
Hagedorn, 330, 332, 381, 425
Hale, 427
Halpin, 378
Hallwass, 138, 143
Haman, 378
Hammarsten, 128
Handovsky, 303
Hanisch, 119, 232, 234, 236, 238, 240, 395
Hanke, 367
Hanssen, 6
Hanusch, 202, 212
Harder, 199, 384
Harper, 164
Harris, 50, 52
Harrison, 108
Hart, 205
Hartmann, A., 424
Hartmann, M., 205, 243
Haskins, 424
Haslewood, 9, 86, 88, 99, 108, 109, 167, 200, 205, 206, 207, 208, 221, 349, 380
Hasselstrom, 68, 343, 344
Hatcher, 299
Hathaway, 378
Haupt, 408, 414, 416, 419
Haurowitz, 190
Hauschild, 195
Hausen, v., 199
Häussler, 198
Hauth, 113, 169
Haworth, R. D., 9, 22, 40, 42, 64, 71, 209
Hawran, 105
Hawthorne, 389
Hayashi, 96
Hecht, 365
Heidelberger, 259, 264
Heilbron, 122, 172, 173, 178, 181, 182, 184, 362, 364, 365, 372, 373, 376, 381, 393
Heinle, 8
Helfenstein, 295
Hell, 70
Hermanns, 258, 261
Hershberg, 98, 106, 110, 221, 343, 347, 355, 387, 388
Hess, 175
Hesse, 127, 303, 307, 308, 419, 421
Hewett, 13, 16, 17, 22, 83, 88, 98, 158, 159, 161, 162, 166, 167, 209, 211, 216, 223, 348, 349, 356, 357, 370, 388, 389
Heyns, 231
Hibbert, 50
Hieger, 16, 82, 83, 87, 88, 349
Higginbottom, 347
Hildebrandt, 195, 200, 206, 213, 226
Hill, 347
Hillemann, 163, 165, 371
Hinkel, 340
Hirano, 236, 237, 240, 394
Hirsch, 34
Hirschmann, 383
Hisaw, 240, 242
Hoffmann, 259, 260, 265, 275, 299
Hofmann, A., 259, 260, 295, 426
Hofmann, K., 422, 423
Hohlweg, 199, 213, 241, 402
Holleman, 15
Holmes, 355
Honeywell, 181
Honigmann, 175, 177, 231
Hooker, 54
Hörlein, 33
Hoshino, 304, 424
Hosking, 64, 68
Hösli, 22, 65, 160, 220, 319, 320, 422, 423
Hossfeld, 157
Houben, 16, 341
Howes, 46, 344
Hromotka, 33, 42
Huang, 5, 12, 71, 389
Hueper, 92, 353
Hummel, 113
Hüttel, 419, 421
Huyser, 59, 60

Iball, 159, 167, 370
Ichikawa, 81
Ikawa, 313
Inhoffen, 157, 172, 173, 176, 182, 402, 405
Ioffé, 8
Irmisch, 20, 21
Ishiguro, 347
Ishiwata, 43
Isler, 423
Iwasaki, 366

Jackson, 374
Jacobi, H., 199
Jacobi, R., 126, 136, 139, 146
Jacobs, W. A., 164, 257, 259, 260, 261, 262, 263, 264, 265, 266, 267, 270, 271, 272, 274, 275, 276, 277, 278, 279, 284, 285, 287, 288, 289, 291, 294, 299, 322, 324, 327, 328, 329, 336, 408, 412, 413, 417
Jacobsen, 341, 342, 424, 426, 427
Jakubowicz, 115, 401
Jänecke, 22
Janot, 199
Japp, 15
Jarlov, 191, 200
Jenkins, 179
Jensen, 30, 303, 312, 313, 314, 316, 419, 421
John, 105
Johnstone, 373
Jones, D. M, 404
Jones, R. N., 374, 376
Jongh, de, 193, 195, 202, 213, 218
Jurs, 425

Kaffer, 16
Kägi, 239, 395
Kahn, 132
Kahnt, 191
Kamm, E. D., 178, 181
Kamm, O., 230, 363, 387, 397, 404
Kamp, van de, 9, 10, 12, 344, 348
Kapitel, 138
Kardos, 5
Karrer, 416
Karstens, 58, 158, 167
Katsura, 424
Katzman, 190, 193
Kaufmann, C., 215
Kaufmann, H. P., 118, 324
Kawai, 138
Kawasaki, 359
Kaziro, 126, 127
Kazuno, 366, 367
Kōimatsu, 347
Keller, 365
Kendall, 406
Kennaway, 82, 83, 87, 88, 349
Kenner, 6
Kesler, 50
Kethur, 341
Kiliani, 324
King, F. E., 341
King, H., 133, 149, 151, 160, 196
Kipphan, 171
Kirchner, 157
Kishi, 127, 367
Kitasato, 38, 43, 320, 423
Klänhardt, 323
Klare, 165, 167
Klein, 404
Klenk, 364
Kletzien, 378
Klinger, A., 96
Klinger, H., 15
Knecht, 50
Knick, 274, 288
Knock, 41
Knorr, 33
Kobayashi, 314
Kober, 193, 194, 195
Koch, E. M., 378, 380
Koch, F. C., 192, 224, 237, 378, 380, 394
Kofler, A., 195
Kofler, L., 318
Kögl, 22, 24
Kohler, 71, 174
Komppa, 72
Kon, 160, 164, 165, 262, 292, 388, 425, 427, 428
Kondo, 37, 38, 43, 313
König, G., 128
König, O., 130
Konz, 304
Koralek, 35
Körding, 115, 149, 158
Korenchevsky, 237, 396
Köser, 179, 182
Kotake, 159, 312
Kraft, 68, 345
Kraus, J., 392
Kraus, K., 365, 424
Kreis, 259, 260
Kreuger, H., 344
Kreuger, J. W., 342, 344
Krishna, 42
Kruber, 17, 64
Kudszus, 232, 234, 236, 403
Kuhn, 182
Kulenkampff, 140
Kuntze, 42
Kunz, J., 8
Kunz, M., 8
Kuwada, 394, 395, 424
Kyogoku, 127

Lacassagne, 218
La Lande, 59
Lamb, 408
Lampe, 344
Lange, 193
Langer, 180, 372
Laquer, 181
Laqueur, 193, 194, 195, 213, 218, 237, 238
Larsen, 100
Lassar-Cohn, 143
Laucht, 154, 373
Laucius, 363, 387, 397
Lawrence, 109, 223, 348, 356, 390
Lawson, 216, 385, 386
L'Ecuyer, 341
Lehmann, Eduard, 259
Lehmann, Erich, 223
Leonard, 242
Lettré, 180, 182, 381, 398, 405
Leuenberger, 424
Levin, 200, 206, 215, 385
Levy, 51, 59, 60
Lévy, 65, 80, 348
Lewaschowa, 358
Lewis, 21
Liang, 324
Lieb, 22, 97
Liebermann, 1, 5, 18, 70, 117
Liégeois, 88
Lifschütz, 117, 361
Linn, 134
Linsert, 174, 179, 181, 324, 326, 381
Lobb, 378
Locher, 205
Loeb, Leo, 218
Loewe, 193, 218, 244
Lombardi, 19
Lothrop, 74
Löwenstein, 8
Lowy, 50
Luchs, 244
Ludewig, 12
Lumpp, 11
Lüttringhaus, 171, 172, 173, 174, 179, 373

Lutz, 343
Lux, 56

Ma, 223, 391
MacCorquodale, 194, 197, 207, 214, 215, 385
Macht, 302
MacLachlan, 405
Maisin, 88
Malmberg, 200
Mamoli, 248, 249, 250
Mannich, 16
Marker, 230, 362, 363, 387, 396, 397, 404
Marrian, 194, 197, 200, 201, 202, 205, 206, 207, 208, 382
Martin, 72, 347, 389
Marvel, 356
Marx, 368
Mason, 406
Massengale, 378
Matsukawa, 393, 395, 397, 403, 424
Matsuzaki, 237
Mauron, 62
Mauthner, 134, 180, 362, 371
Mavrodineanu, 341
Mavin, 9, 22
Maxim, 341
Mayeda, 374
Mayer, E. W., 114
Mayer, F., 6, 30, 97, 354
Mayneord, 84, 88, 159, 166, 167, 349
McDonald, 380
McFadyen, 341
McGee, 192
McGrew, 404
Meerwein, 361
Meier, 65
Menschick, 152
Merk, 324
Meyer, H., 127, 307
Meyer, Hans, 265
Meyer, J., 50, 59, 60, 61, 62, 115, 226, 230, 234, 235, 240
Meyer, R. K., 195, 202, 242
Micheel, 261
Miescher, 396
Miller, 195
Milt, de, 342
Mincovici, 255
Mittasch, 303, 304
Miyasaka, 394
Mohs, 424
Moldenhauer, 134
Moll, 177
Möller, E. F., 182
Möller, K., 220
Moore, C. R., 192
Morato-Manaro, 405
Morgan, G. T., 102, 108
Morgan, W. M., 429
Mörgeli, 424
Morris, 344
Morrison, 138, 172, 373
Mortimer, 5
Morton, A. A., 92, 352
Morton, R. A., 178, 181, 362
Mosettig, 9, 10, 11, 12, 14, 17, 342, 343, 344, 348
Müller, Ernest, 125, 341
Müller, Eugen, 343
Müller, H., 5, 12, 71
Müller, H. J., 64
Müller, M., 174, 182
Müller, P., 354
Münch, 237
Murke, 374
Murphy, 5
Myers, 406

Nabenhauer, 112, 118
Nakajima, 38
Natelson, 360, 391
Nedswedski, 357
Nenitzescu, 370
Neracher, 380
Nesty, 356
Neubauer, 357
Neuhaus, 243
Neukirchen, 127, 136
Neumann, 409
Newman, 86, 88, 98, 130, 353, 413, 417
Niederländer, 172, 231, 359
Niven, 352
Noller, 319, 320, 324, 425
Northup, 205
Novak, 215
Nozoe, 424
Nussmeier, 378
Nyka, 218
Nyman, 344

Oakwood, 362, 363, 387, 397, 404
Oberlin, 39
Ochiai, 37
Oda, 127
Odell, 382
Offe, 312, 421, 422
Ogata, 236, 237, 240
Ogawa, 343
Okamura, S., 125
Okamura, T., 125, 126, 127
Olberg, 100
Openshaw, 341
Oppenauer, 234
Oppenheimer, 97
Orékhoff, 79
Ormston, 162
Osada, 39, 43
Ostermayer, 1
Ottawa, 365, 369
Otten, 130
Oyster, 14

Paasche, 223
Page, 152
Palkin, 50, 52

Parkes, 196, 396, 397, 404
Parry, 381
Parsons, 352
Pascal, 4
Peak, 389
Pence, 9
Perkin, W. H. jun., 40
Perlman, 348
Peters, 71, 74, 94, *see* M. Fieser
Petrow, 159, 358
Petru, 158
Peyer, E., 159
Peyer, J., 295, 426
Pézard, 224
Pfeiffer, 60, 340
Pfiffner, 406
Philpot, 179
Phipers, 122, 173
Phisalix, 303
Pinckney, 356
Pincus, 382, 387
Pohl, 178
Polak, 396
Popkin, 363
Porges, 357
Posternak, 148, 153
Power, 324
Pregl, 143
Price, 7, 339, 340, 341, 342, 355
Pschorr, 28, 29, 32, 40

Quietensky, 39

Rabald, 405
Rabe, 76
Radcliffe, 71
Ragins, 378
Ramage, 21
Ramirez, 393
Rankin, 40
Ransom, 322
Raper, 429
Rapson, 30, 222, 389
Rauch, 372
Raudenbusch, 218
Raudnitz, 158
Reichel, v., 157, 172, 375
Reicheneder, 419
Reichstein, 380, 384, 406
Reid, 344
Reindel, 171, 172, 231, 369, 372
Reinhold, 360
Reinitzer, 426
Reintke, 62
Reiss, 190
Rekner, 8
Remesow, 358
Resau, 136
Revery, 126
Rheinboldt, 130
Richter, 195
Rickert, 165
Riegel, B., 397
Riegel, C., 360
Rilliet, 100
Ristic, 343
Rittenberg, 123, 405
Ritter, 345
Rivero, 394
Rivkin, 74
Robinson, (Mrs.) A. M., 108, 221
Robinson, F. A., 379
Robinson, (Mrs.) G. M., 222
Robinson, R., 21, 24, 30, 35, 44, 45, 222, 225, 389, 390
Robinson, R. A., 344
Roblin, 78
Roe, 84, 159, 166, 167, 213
Rogoff, 406
Rohrmann, 72
Rondoni, 88, 405
Rose, 360
Rosenberg, 240, 395, 404
Rosenheim, 117, 123, 133, 149, 151, 160, 178, 196, 373
Ross, 43
Rothen, 274
Rousselot, 405
Ruggli, 343
Ruhkopf, 424
Ruschig, 242, 243, 245
Rutgers, 195, 201
Rutz, 195
Ruzicka, F. C. J., 164, 388
Ruzicka, L., 22, 50, 51, 52, 53, 58, 59, 60, 61, 62, 64, 65, 66, 68, 70, 75, 113, 115, 158, 159, 160, 167, 220, 226, 229, 230, 233, 234, 235, 238, 239, 240, 318, 319, 320, 327, 345, 363, 395, 396, 401, 403, 404, 422, 423, 424
Rygh, 178, 180

Saastamoinen, 199
Saito, 343
Salkowski, 117
Salway, 324
Samant, 173, 182, 376
Sandermann, 345
Sandqvist, 5, 8, 169, 427
Sandulesco, 195, 197, 201, 213, 383
Saunders, 165
Schapschinskaja, 63
Scharrer, 199, 384
Schellenberger, 423
Schenck, Fr., 180, 374, 379
Schenck, M., 381
Schering-Kahlbaum A.-G., 213
Schicke, 320
Schilling, 2
Schindel, 113
Schinz, 51, 61, 70
Schlichting, 85, 138, 143, 145, 146, 167
Schlittler, 40, 42, 222
Schmidt, E., 4, 19
Schmidt, Josef, 243, 246, 248, 251, 395, 402, *see* Schmidt-Thomé

Schmidt, Julius, 8, 11, 15
Schmidt, R., 361
Schmidt-Thomé, 359, 395, 404
Schmulovitz, 382
Schneckenburger, 321, 324
Schoeler, 39
Schoeller, 199, 213, 226, 234
Schoenheimer, 113, 115, 117, 119, 121, 122, 123, 282, 359, 360, 361, 365, 370, 384, 398, 405
Scholl, 6, 16, 93
Scholz, 139, 155
Schön, 19, 98, 101
Schoor, van, 126
Schöpf, 34, 37, 44
Schramm, 221, 402, 403
Schramme, 30
Schroeter, 5, 12, 71
Schropp, 199, 384
Schrötter, 26, 27
Schulenberg, 143
Schulte, 403
Schultz, 1, 14
Schultze, 56
Schulze, G., 173
Schulze, H., 358
Schürch, 88, 91
Schwarte, 259
Schwarzer, 6
Schwarzkopf, 126
Schwechten, 342
Schweissinger, 324
Schwenk, 195, 213, 226, 383, 385
Schwieger, 299
Scott, 266
Seer, 100
Seidel, 59, 60
Sekitoo, 131
Seligman, 105, 106, 107, 354
Sengupta, 13, 76
Serini, 234
Setz, 181
Sexton, 362, 372
Shah, 324, 333
Sharp, 343
Shear, 87, 349
Sheldrick, 209
Sherwood, 71, 356
Shimizu, 128, 366, 367
Shimodaira, 304
Shishido, 343
Shoda, 127
Shoesmith, 11
Shoppee, 11
Short, 71, 347, 357
Shrader, 424
Shriner, 112
Siebert, 79
Siemiradzki, v., 62
Sifferd, 365
Silberbach, 40
Silberschmidt, 42
Simon, 344
Simons, 380
Simpson, J. C. E., 172, 324, 327, 328, 329, 336, 373
Simpson, S. L., 237
Skarzynski, 199
Slotta, 242, 243, 244, 245
Small, 24, 34, 37, 38, 46, 343
Smellie, 43
Smith, E. R., 205
Smith, R. G., 344
Smith, S., 259, 276, 283, 299, 408, 409, 410
Smith, W. E., 344
Sobel, 360
Sobotka, 130, 132, 133, 368
Soltys, 428
Sone, 424
Sonn, 341
Sorge, 129
Späth, 33, 39, 41, 42
Sperry, 357, 360
Spiegel, 70
Spilker, 20
Spring, 122, 173, 182, 184, 364, 365, 373, 376, 381, 393, 423
Stadler, 158
Stählin, 40
Stamatoff, 78
Stange, 155, 380
Starup, 121
Staub, 343
Steele, 51
Steenbock, 378
Stein, 179, 182, 259, 272, 276
Stephen, 341
Stewart, G. N., 406
Stewart, P. A., 182
Stevens, 341
Stodola, 365
Stoll, 259, 260, 295, 299, 363, 426
Störmer, 195, 199, 201, 206, 384
Strasser, 70
Straub, 299
Strauhal, 42
Stromberg, 347, 357
Struve, 340
Suckfüll, 374
Sugasawa, 45
Suida, 180, 362, 371
Sumi, 347
Sumuleanu, 28
Suter, 259
Swingle, 406
Szent-Györgi, 119

Tanaka, 236
Tausk, 244
Tchung, 201
Teodoro, 384
Tharrer, 41, 42
Thayer, 193, 194, 197, 200, 201, 206, 207, 214, 215, 385
Thaysen, 119
Thiele, W., 182, 185

Thomann, 113, 158, 167
Thompson, H., 168, 207, 208
Thompson, H. W., 222
Tien, 223, 391
Tiffeneau, 79
Tincker, 384
Trautmann, 185, 371
Treibs, 371
Trommsdorff, 53
Tscherning, 119, 224, 225, 232, 235, 237, 240, 396
Tschesche, 128, 152, 262, 274, 283, 284, 288, 289, 312, 318, 328, 330, 332, 358, 408, 409, 410, 413, 414, 416, 419, 421, 422, 424, 425
Tschopp, 238, 396, 397
Tschugajeff, 117
Turner, 6
Twort, 91
Tzoni, 379

Uibrig, 115, 116, 134
Urushibara, 403
Utzino, 424

Vadasz, 343
Vanghelovici, 255, 358, 381
Van Zandt, 342
Vars, 406
Vasiliu, 381
Vavon, 115, 401
Veen, van, 327
Veler, 193
Verdollin, 382
Vesterberg, 53, 427
Vetter, 19, 88, 98
Vilim, 50
Virtanen, 199
Vocke, 62, 68, 148, 151, 153, 305
Vogel, 21
Vogt, A., 11
Vogt, G., 418
Volk, 132
Vongerichten, 26, 27, 28
Vorländer, 79
Voss, H. E., 193, 218, 226, 244, 392, 405
Voss, W., 418

Wack, 8
Waddell, 378
Wagner-Jauregg, 363
Wahlforss, 54
Wähner, 193
Waldmann, 58, 65, 70, 75, 94
Walker, J., 222, 389, 390
Wallach, 79
Wallenfels, 428
Wallenstein, 105
Wallis, 229, 234, 236, 358, 364
Walter, E., 372
Walter, R., 2
Wang, 403
Warnat, 39
Warren, 236
Webster, 123, 178, 179
Wedekind, 320, 424
Weidlich, 110, 168, 179, 207
Weil, 127, 135, 306, 325
Weinhold, 323
Weiss, 79
Weissgerber, 64
Weitzenböck, 16, 22, 96, 97
Weizmann, 72, 94
Werder, v., 169, 177, 179, 231, 379, 426
Werner, A., 8
Werner, L., 363
Werthessen, 387
Westphal, K., 259, 272
Westphal, U., 194, 206, 207, 241, 246, 251, 402, 404
Westphalen, 157
Wettstein, 234, 238, 239, 243, 396
Weyland, 125, 126, 150, 307
Wheeler, 382
Whitby, 117
White, 46
Whitman, 383, 385
Whitmore, 230
Widmer, 82
Wiedersheim, 85, 167
Wieland, H., 35, 85, 125, 126, 127, 129, 132, 133, 135, 136, 138, 139, 140, 143, 145, 146, 147, 148, 150, 153, 154, 155, 156, 167, 168, 303, 304, 305, 306, 307, 308, 365, 367, 369, 419, 421, 424
Wienhaus, 345
Wiese, 374
Wignall, 276
Wiles, 347, 357
Wiley, 356
Willerding, 324, 325
Willgerodt, 9
Willig, 6
Willstätter, 114
Windaus, A., 30, 38, 113, 115, 116, 118, 119, 126, 127, 128, 133, 134, 135, 136, 140, 152, 155, 157, 169, 171, 172, 173, 174, 176, 178, 179, 180, 182, 258, 259, 261, 272, 276, 279, 283, 289, 299, 321, 322, 323, 324, 325, 326, 329, 333, 358, 371, 372, 373, 374, 377, 379, 380, 403, 426, 427
Winterstein, 19, 88, 91, 98, 101
Wintersteiner, 242, 245, 383, 385, 406
Wirz, 230, 233, 403
Wislicenus, 134
Wittig, 341
Wittle, 363
Wizinger, 340
Wolfe, 386
Wolfes, 28
Wolff, 250, 403
Wolter, 173
Woodcock, 357
Wright, C. I., 344

Wright, H. R., 122
Wunderlich, 381
Wylie, 382

Yago, 395
Yamagiwa, 81
Yamasaki, 127, 132, 368
Yoder, 378
Yokayama, 159
Yoshida, 352
Young, F. E., 379
Young, F. G., 359
Young, G., 382
Young, L. E., 402
Young, M. N., 3, 347
Young, P. G., 21
Yuen, 343
Yuuki, 368

Zahl, 382
Zampetti, 384
Zechmeister, 374
Zelinsky, 177
Ziegner, v., 191, 193
Zimmermann, 195
Zondek, 192, 196, 197, 198, 200
Zopf, 22
Zucker, 380

SUBJECT INDEX

Abietic acid, 49-52, 53-54, 345
  dehydrogenation, 53-54, 58, 62
  preparation, 50-52
  structure, 58-66, 346
Abietinal, 65
Abietinol, 62, 65
Absorption, physiological, 121
Absorption spectrum, abietic acid, 68, 346
  aromatic hydrocarbons, 84, 167
  benzenoid rings, 213, 274, 413
  bufotalien, 420
  diene systems, 68, 173, 181, 346, 362, 369, 371, 374
  ergosterol, 173, 371
  levopimaric acid, 68, 346
  oestrogenic hormones, 382
  scillaridin A, 299, 420
  triene systems, 175, 179, 375, 379, 413
  α,β-unsaturated ketones, 152, 239, 245
  unsaturated lactone ring, 299, 420, 421, 422
  vitamin D, 379
  vitamin D_2, 179, 379
Acenaphthene, 93-94
β-1-Acenaphthylethyl bromide, 108, 109
Acetoxycholanic acid, 308
3-Acetoxy-12-ketocholanic acid, 139
Acetoxy lactone, $C_{24}H_{30}O_4$, 291, 292, 293, 294
9-Acetylamino-2,3,4,6-tetramethoxyphenanthrene, 343
Acetyl bufagin, 314
Acetyl bufotalane, 307
Acetyl bufotalien, 307
3-Acetyl desoxycholic acid, 139
Acetyl digitoxin, 261
Acetyl dihydrocholesterol, oxidation, 170, 227
2-Acetyl-9,10-dihydrophenanthrene, 9-10
Acetyl-β-3-hydroxy*allo*cholanic acid, 170, 171
Acetyl-β-3-hydroxynor*allo*cholanic acid, 170, 171, 172
5-Acetyl-1-methylnaphthalene, 73-74
Acetylphenanthrene, 1-, 342
  2-, 9, 10, 163, 342
  3-, 9, 10, 342
  4-, 343
  9-, 10, 342
4-Acetyl-3-phenanthroic acid, 343
6 (or 7)-Acetyl-2-phenanthrol, 14
Acetyl-3-phenanthrol, 6-, 14
  9-, 14
Acetyl thebaol, 29
Acetyl tigogenin, 330, 331
Acid A from digitogenin, 326, 334, 425
Acid B from digitogenin, 333, 334, 425
Actiniasterol, 365
Actinodaphnine, 41, 42
Adrenal cortex, 406-408
Adrenaline, 303
Adrenosterone, 407
Adsorption, chromatographic, 19, 101, 379, 419-420
Aescigenin, 319
Aescin, 319
Aetio*allo*bilianic acid, 289, 330-331
Aetio*allo*cholanone-17, *see* androstanone
Aetiobilianic acid, 147, 168-169
Aetiocholanic acid 146-147, 289
Aetiocholyl methyl ketone, 204
Agathic acid, 68-69
Agathic dicarboxylic acid, *see* agathic acid
Aglycones, *see* cardiac aglycones
Agnosterol, 113, 358
Alcohol $C_{21}H_{36}O_3$ from urine, 205
Aldehyde syntheses, 10-11, 340-341
Aleppic acid, 50
Alkaloids, aporphine, 38-43
  benzylisoquinoline, 43-45
  corydalis, 42, 44
  drug addiction, 45-48
  genetic relationships, 43-45
  morphine, 24-38
  physostigmine, 304
  related to sapogenins, 428-429
Alkyl-1,2-benzanthracenes, 99
o-Alkyl benzophenones, 100
Alkyl phenanthrenes, syntheses, 70-80, 348
Allen-Doisy test, 191-192, 196
*Allo*cholanic acid, 127, 289, 295-296
  configuration, 156
Allocholesterol, 361, 362
"Allocholesterol," 118, 119, 121, 361
Allomerization, 155-156
*Allo*pregnanediol, 205, 404
*Allo*pregnanedione-3,20, 249, 404
  activity, 250-251
  bromination, 249-250
*Allo*pregnanol-3-one-20, isolation, 242, 243, 245, 402
  origin and metabolism, 252, 253
  structure, 248-249
Δ^1-*Allo*pregnenedione, 250, 251
Allopseudocodeine, 34-35
Allo-series, 114
Allothilobilianic acid, 151

Allylic rearrangement, 35, 175, 280
17-Allyltestosterone, 395
Alumina, 19, 101
17-Aminoandrostanol-3(α)-, 396
o-Aminoazotoluene, 352-353
6-Aminocholestane, 381
9-Amino-1,2,5,6-dibenzanthracene, 90
dl-Aminolaudanosine, 40
2-(*p*-Aminostyryl)-6-(*p*-acetylaminobenzoylamino)-quinoline methoacetate, 92, 352
Aminotetrahydro-N-methylpapaverine, *see* *dl*-aminolaudanosine
Amolonin, 324, 425
Analysis of natural products, 426-427
Androstane, 232, 407
Androstanediol-3,17, 235
Androstanedione-3,17, 232, 235, 240, 404
Androstanol-17-one-3, 240
Androstanone-17, 233, 235, 407
Androstenediol-3,17, 238, 239, 240, 397
Δ^{1}-Androstenedione-3,17, 397
Δ^{4}-Androstenedione-3,17, physiological actions, 236, 238, 397
  preparation, 236
  rôle in metabolism, 253, 254
  from testosterone, 239
Δ^{4}-Androstenetrione-3,6,17, 397
Androstenol-17-one-3, *see* testosterone
Δ^{5}-Androstenolone acetate, 396
Androstenone, 233
Androsterone, 188
  activation by X-substance, 396-397
  bio-assay, 224, 383, 396
  characterization, 225-226, 231-232
  configuration, 229
  derivatives, 234-236, 396
  isolation, 224-226
  oestrogenic activity, 236, 397-398
  origin and metabolism, 252, 253-254
  preparation from cholesterol, 226-231
Angelica lactones, 265-266
Anhydrobufotalonic acid, 309
Anhydrodigitoxigenin, 300, 409-410
Anhydrodigitoxigenone, 411
Anhydrodihydrostrophanthidin, 285-286, 412-413
Anhydrogamabufogenin, 305, 311
γ-Anhydroisogitoxigenic acid, 279, 280
Anhydro-α-isostrophanthonic dimethyl ester, 271
Anhydrosarmentogenin, 410
Anhydroscillaridin A, 295-296
Anhydroscillaridinic acid, 296-297
Anhydrostrophanthidin, 270, 271, 274
  hemiacetal, 270-271
Anhydrostrophanthidinic ester, 269
Anhydrostrophanthidonic ester, 269
Anhydro-uzarigenin,α-, 259, 284, 285, 288, 300
  β-, 284, 300
Aniline cancer, 92, 353
Anthracene, 2-3, 100
Anthropodesoxycholic acid, *see* chenodesoxycholic acid
Antiarigenin, 419
Antiarins, 418-419
Antirachitic activity, 177-181
  and structure, 380-381
Apocholic acid, 132, 368-369
β-Apocholic acid, 369
Apomorphine, 31-33
Aporphine group, 38-43
Arabinose, 319
Arenobufagin, 316, 421
β-Aroylpropionic acids, 71, 72
Aschheim-Zondek reaction, 190
Atherosclerosis, 121
Auwers-Skita rule, 116-117

Bardhan synthesis, 220, 387-388
Bardhan-Sengupta synthesis, 76-77, 108, 109, 160-161, 220
Beckmann rearrangement, 11, 342
Benzaldehyde-choleic acid, 132
1,2-Benzanthracene, 82, 83, 84, 93, 97
  derivatives, 88-90, 349-351
ang.-Benzanthracenes, 93-94
Benzanthrene, 91
1,2-Benzanthroic acid, 97
1,2-Benz-10-anthrone, 354
1,2-Benzcarbazole, 19, 20
15,16-Benzdehydrocholanthrene, 107, 350
Benzilic acid rearrangement, 15, 55, 144
1,2-Benznaphthacene, 20
Benzoylphenanthrene, 1-, 9, 10, 342
  2-, 9
  3-, 9
  9-, 10
3,4-Benzphenanthrene, 91, 97, 110, 355
3,4-Benzphenanthroic acid, 97
1,2-Benzpyrene, carcinogenic action, 84, 88, 90, 349, 351
  isolation, 83-84
  nomenclature, 16, 349
  oestrogenic action, 217
  synthesis, 98
3,4-Benzpyrene, 349, *see* 1,2-benzpyrene
4,5-Benzpyrene, 84, 89, 99
Benzylisoquinoline alkaloids, 43-45
17-Benzyltestosterone, 395
Berberine, 44
Betaine-hydrazide hydrochloride, *see* Girard's reagent
Betulin, 320, 423
Bile, 123, 366
Bile Acids, 123-129, 366-368
  analysis, 366
  choleic acids, 129-132, 368, 369
  configuration, 231, 369
  conjugated, 123, 124-125, 366
  degradation of side chain, 146
  dehydration, 124, 365-366
  dehydrogenation, 149, 158-159, 370
  function, 123

Bile Acids, old formula, 147-148
  origin, 251, 252, 255
  position of side chain, 167-168
  revision of formula, 148-152
Bile salts, 123
Bilianic acid, 140, 143, 144
Bilirubin, 123, 125
Biloidanic acid, 142, 144
Biogenetic relationships, *see* genetic relationships
Bis-*ang*.-dibenzanthracenes, 93, 94-96
Bischler-Napieralski reaction, 33, 41, 221
Bisnor*allo*cholanic acid, 170, 289
Bisnorcholanic acid, 146, 367
  degradation to pregnane, 204
Bisnorlithocholic acid, 231
Bistrzycki rule, 62-63, 153
Blanc reaction, 106
  rule, 140-141, 145, 151, 327
Bogert-Cook synthesis, 348, 370, *see* Perlman-Davidson-Bogert synthesis
Boldin, 39, 40-41
Bombicesterol, 359
Boswellinic acid, 319
Bougault reaction, 220, 221, 223
Bouveault reduction, 62
  synthesis, 341
Brazan, 20
Bromination, cholestenone, 402-404
  oriented, 249-251, 402
  phenanthrene, 6-7, 339-340, 341
  steroid ketones and keto acids, 402-404
2-Bromoandrostanedione-3,17, 397
2-Bromo-5-chloroandrostanedione-3,17, 398
6-Bromo-Δ^4-cholestenone, 403
1-Bromo-4-methoxynaphthalene, 388
1-Bromo-5-methoxynaphthalene, 388
4-Bromo-7-methylhydrindene, 106, 354
9-Bromophenanthrene, 7, 339, 340
Bufagin, 302, 303, 308, 314-315, 422
Bufaginic acid, 314
Bufagins, 303, 315-316, 421
  activity, 305-306
  isolation, 306
Bufosterocholenic acid, 366
Bufotalane, 307
Bufotalanone, 307, 310
Bufotalidin, 421
Bufotalien, 304, 305, 307, 310, 311, 420
Bufotalin, 304, 305, 306-311, 419-421
Bufotalinin, 421
Bufotalone, 307, 309
Bufotenidine, 303, 304
Bufotenine, 303, 304, 306, 419
Bufotoxin, 304-305, 310, 420
Bufotoxins, 303, 304, 305-306
Bulbocapnine, 42

Calciferol, *see* vitamin D_2
Calotropagenin, 419
Calotropin, 419
Camelliasapogenin, 319
Cancer, 81
  aniline, 92, 353
  coal tar, 81-85, 92-93
  mustard gas, 92
  and oestrogenic hormones, 217-218, 352
Cancer-producing hydrocarbons, 81-110
  comparison of activity, 88-93, 349-352
  synthesis, 93-110
  test methods, 86-88
Capon test, *see* comb growth test
  unit, 224
3-Carbethoxyandrosterone, 397
2-Carbethoxycyclohexanone, 356
Carboxymethoxylamine, 384
Carboxy-3-phenanthrol, 2-, 14
  4-, 14
p-Carboxyphenylhydrazine, 384
Cardiac aglycones, 258, 259
  anhydro compounds, 284, 409, 410, 412-413
  carbon skeleton, 285-287, 288-290, 295-296
  configuration, 285, 290, 300-301, 409, 410, 412, 413
  dehydration, 261-262, 280-281, 284
  dehydrogenation, 287-288
  iso-compounds, 266-267, 277, 283, 284, 291, 410, 414, 416
  isomerization, 266, 267, 270, 277, 278-279, 279-280, 283, 284, 291
  lactone ring, 265-268, 296, 301, 408-409
  molecular weights, 408-409
  physiological activity, 299-302
  structures, 262-263
Cardiac glycosides, 256-261, 290-291, 408
  extraction and purification, 258
  hydrolysis, 258-262, 415, 418
  physiological activity, 256-257, 299-302, 411-412, 415-416, 417-418
  sugars, 259, 261
Carotene, 240, 255
Caryocarsapogenin, 319
Cerin, 424
Ch'an Su, 302, 303, 312-314
Chenodesoxycholic acid, 123, 124, 125, 126, 127, 366
Chloro*allo*cholanic acid, 3(α)-, 392
  3(β)-, 392
Chloro*allo*cholanic acid, 3(α)-, 392
  3(β)-, 392
Chloroandrostenone, 232, 393
Chloroandrosterone, 233
  α-, 230, 233, 392
  β-, 230, 392
Chlorocodide, α-, 34, 35
  β-, 34, 35
Chlorogenin, 324, 327, 429
5-Chloroisoandrosterone, 397
Chloromethyleneformamidine, 341
4-Chloro-7-methylhydrindene, 354
$\Delta^{2,11}$-Choladienic acid, 366
$\Delta^{4,6}$-Choladienic acid, 369
Choladienic acids, 124

Cholanic acid, 124, 127, 136-137, 146, 156
Cholanthrene, 90, 349
  syntheses, 99, 106, 108-109
Cholanthrone, 109
Cholatrienic acid, 124, 158
"Choleic" acid, 129-130
Choleic acid principal, 131, 368
Choleic acids, 129-132, 368, 369
Cholenic acid, Δ^2-, 124, 366
  Δ^3-, 124, 366
  Δ^5-, 366
  Δ^6-, 366
  Δ^7-, 366
Cholestadiene-3,5-ol-3, 403
$\Delta^{4,6}$-Cholestadienone, 403
Cholestane, 114
  configuration, 113-114
  oxidation, 136
  preparation, 134
Cholestanedione-3,6, 157-158, 403
Cholestanetriol-3,5,6, 157
  -3,6,7, 335
α-Cholestanol, 392
β-Cholestanol, 392, 409, *see* dihydrocholesterol
4-Cholestanol, 120, 335, 428
Cholestanone, 115, 116, 384, 403
Cholestene, 134
Δ^4-Cholestenedione-4,6, 402
Δ^5-Cholestenedione-3,4, 402, 403
Δ^4-Cholestenone, bromination, 403
  hydrochloride, 134
  oxidation, 152
  preparation, 115, 359
  reduction, 116, 282, 361
  role in metabolism, 123, 255
  separation, 384
Δ^5-Cholestenone, 359, 363
  dibromide, bromination, 402-403
Cholesterol, 111, 113
  biological degradations, 122-123, 186, 251-252, 255, 405-406
  colloidal solution, 357
  conversion to androsterone, 226-230
  dehydration, 362
  dehydrogenation, 149, 166, 371
  dibromide, 113, 115, 120, 134
  digitonide, 118-119, 332, 361
  function, 122
  irradiation, 178, 378
  isomers, 361-364
  methyl groups, 152-154, 371, 387
  microdetermination, 360-361
  occurrence, 112-113, 303, 357
  origin, 120-121, 122, 255, 405
  oxidation of side chain, 135-136, 227
  preparation, 112-113, 358
  purification, 113, 119
  revision of old formulas, 148-152
  structure, 154-158
  tigonide, 424
"β-Cholesterol," 361
i-Cholesterol, 364
Cholesteryl acetate, 119, 136, 157, 364
  dibromide, 234, 393-394
i-Cholesteryl acetate, 364
Cholesteryl chloride, 134, 157, 230, 363, 364, 392
Cholesterylene, 362, 363
Cholesteryl esters, 112, 357
Cholesteryl ethers, 363-364
Cholestyl chloride, 157
  α-, 230, 392-393
  β-, 230, 392-393
Cholic acid, 111, 124, 126
  dehydration, 124, 132, 282
  dehydrogenation, 158-159
  3,7-diacetate, 138, 139
  isolation, 125
  molecular compounds, 129
  occurrence, 123, 124
Choloidanic acid, 141, 142, 145
Chromatographic adsorption analysis, 19, 101, 379, 419-420
Chrysene, 16, 18, 389
  carcinogenic action, 91
  from natural products 149-150, 158, 208, 308
  purification, 18-20
  reactions, 343
  synthesis, 20-22, 110, 162-163, 355
Chrysofluorene, 91, 162,
Chrysogens, 18-20, 101
Chuang syntheses, 391
Cilianic acid, 143-144
Ciloidanic acid, 144
Cinchol, 113, 229, 231
Cinobufagin, 312-313, 314, 421-422
Cinobufagone, 421
Clauberg test, 241-242, 402
Clemmensen reduction, modified, 72, 137, 347, 389
Coal tar, cancer, 81-85
  chrysogens, 18-20
  hydrocarbons, 1, 4, 16-22, 83-84
Cobalt resinate, 52
Codechol, 132
Codeine, 24, 25, 26, 34, 35
Codeinone, 25, 34, 37
Colchicine, 38, 343
Colophony, *see* rosin
Color reactions, cardiac aglycones, 265, 408-409
  ketones, 383
  oestrogenic hormones, 194-195, 202, 382
  sterols, 117, 118
Convallamaretin, 418
Convallamarin, 418
Convallarin, 418
Convallatoxigenin, 416-417
Convallatoxin, 416-418
Comb growth test, 224, 236-237
Copal, 49
Coprostane, 113-114, 134, 136-137
Coprostanone, 115-116, 123, 384
  -4,5d_2, 123, 405

Coprosterol, 113
  digitonide, 119
  occurrence, 122-123
  oxidation, 141, 228
  preparation, 115, 116
Corner-Allen test, 241, 402
Corpus luteum hormone, *see* progestin, progesterone
  bio-assay, 250-251, 402
  function, 189, 240-242
  specificity, 250-251, 404-405
Cortin, 406
Corydaline, 44
Corydalis alkaloids, 42
Corydine, 42
Corytuberine, 42
Coxcomb test, *see* comb growth test
9-Cyanophenanthrene, 342
Cyclamiretin, 319
Cyclization, Bischler-Napieralski, 33, 41, 221
  Blanc rule, 140-141
  Bougault, 220, 221, 223, 387-388
  by Darzens reaction, 390, 391
  mechanism, 78, 348
  pyrolytic, 99
  reagents, 72, 98, 161, 222, 356
Cyclodehydration, 78, 79, 107, 356, *see also* Elbs reaction
Cyclohexanespirocyclopentane, 162
Cyclohexanone-2-acetic ester, 356
Cyclohydration, 356
Cyclopenteno-1,2-benzanthracene,5,6-, 88-89, 102, 217
  6,7-, 102
1,2-Cyclopentenophenanthrene, 160-161
Cyclopentenotriphenylene, 370
Cymarin, 258, 259, 260, 300, 417-418
Cymarose, 258, 259, 260, 261
Cystic mastopathy, 218

Darzens reaction, 390, 391
Darzens synthesis, 79-80, 348
Debromination, 115, 234, 236, 246, 359, 404
Dehydration (*see also* cyclodehydration)
  allocholesterols, 282, 361, 362
  bile acids, 124, 365-366
  cholesterol, 362
  *epi*cholesterol, 363
  β-hydroxyketones, 157, 172, 277-278
  oestriol, 200
  α,β-unsaturated alcohols, 26, 175, 280-282, 293, 298, 311, 315, 362
  Wagner-Meerwein, *see* rearrangements
Δ^1-Dehydro-Δ^4-androstenedione-3,17, 398
Dehydrochenodesoxycholic acid, *see* 3,7-diketocholanic acid
7-Dehydrocholestene, 371
7-Dehydrocholesterol, absorption spectrum, 374
  irradiation product, 181, 377, 378, 379, 380
7-Dehydrocholesterol, preparation, 180-181
  reactions, 374
Dehydrocholic acid, 137, 138, 143-144
  biological reduction, 127-128
Dehydrodesoxycholic acid, 138, 367
  oxidation, 140
  reduction, 167
Dehydroergosterol, 175-176, 413
Dehydrogenating agents, aluminum chloride, 7
  copper oxide, 115
  mercuric acetate, 175, 373, 375
  palladium charcoal, 58, 70, 149, 346
  phenanthrenequinone, 105
  platinum black, 108, 163, 388
  selenium, 58, 149, 158, 159, 358, 391, 424, 428, 429
  selenium dioxide, 369, 373
  sulfuric acid, 160, 161
  zinc, 98, 208
Dehydrogenation, abietic acid, 53, 58, 62
  agathic acid, 69
  bile acids, 158, 371
  bufotalin, 308
  cardiac aglycones, 287-288
  cinobufagin, 313
  equilin, 212-213
  ergosterol, 373
  α-ergosterol, 373
  fichtelite, 70
  hydrindenes, 159, 370
  isoagathic acid, 69
  ketotetrahydrobenzpyrene, 98
  lanosterol-agnosterol, 358
  neoergosterol, 177
  octahydrophenanthrene, 76
  oestrone, 208
  onocerin, 359
  d-pimaric acid, 66
  pseudobufotalin, 313
  solanthrene, 428
  solanocapsidine, 429
  sterol-like sapogenins, 327-328
  sterols, 159, 166, 167
  synthetic acids, 65
  tetrahydrolevopimaric ester, 346
  triterpene alcohols, 319
  triterpenoid sapogenins, 318-320
Dehydrohyodesoxy*allo*cholic acid, 155
Dehydrohyodesoxycholic acid, 155
Dehydroisoandrosterone, 232-234
  dibromide, 236
  origin and metabolism, 251, 252, 253, 255
  physiological activity, 235, 236, 240, 397
  reduction, 238, 239
Δ^4-Dehydroisoandrosterone, 240
Dehydrolumisterol, 375
Dehydroneoergosterol, 177, 219, 387
Dehydronorcholene, 167, 168, 352
7-Dehydrositosterol, 381
7-Dehydrostigmasterol, 381
2-Demethylglaucine, 43

Dephanthanic acid, 272, 273
Dephanthic acid, 272, 273
Desacetyl digilanide A, 261
Desoxybilianic acid, 140-141, 142, 143
Desoxycholic acid, 123, 124, 125, 126, 366
  3-glucoside, 382
  molecular compounds, 129-132
  old formula, 148
  purification, 131
Desoxycodeine, 344
(3)-Desoxyprogesterone, 251
Desoxysarsasapogenin, 336, 337
3,5-Diacetoxycholestanone-6, 374
9,10-Dialkyl-9,10-dihydroxy-9,10-dihydro-1,2,5,6-dibenzanthracenes, 216, 385-386
9,10-Dialkyl-9,10-dihydroxy-9,10-dihydro-1,2,5,6-dibenzanthracene, 386
9,10-Di-*n*-amyl-9, 10-dihydroxy-9,10-dihydro-1,2,5,6-dibenzanthracene, 216, 386
Dianhydroantiarigenin, 419
Dianhydrobufagin, 314, 315
Dianhydrodihydrogitoxigenin, 280
Dianhydrogitoxigenin, 259, 262, 279, 280-281
Dianhydro-α-isoperiplogonic ester, 276
Dianhydrostrophanthidin, 274
Dianhydrostrophanthidonic ester, 269
Dibasic lactone acid, $C_{22}H_{32}O_6$, 327, 332, 428
Dibenzacridine, 1,2,5,6-, 91
  3,4,5,6-, 91
bis-*ang.*-Dibenzanthracenes, 93, 94-95
1,2,5,6-Dibenzanthracene, carcinogenic action, 83, 86-87, 88, 349
  -choleic acid, 88
  derivatives, 90, 216, 385-386
  9,10-endo-α,β-succinic acid, 88, 352
  preparation, 96-97, 100-101, 355
  purification, 101
1,2,6,7-Dibenzanthracene, 101
1,2,7,8-Dibenzanthracene, 94-95, 97, 103
2,3,6,7-Dibenzanthracene, 89, 105.
Dibenzanthraquinone, 1,2,5,6-, 90, 95, 96
  1,2,6,7-, 96
  1,2,7,8-, 96
3,4,5,6-Dibenzcarbazole, 353
3,4,5,6-Dibenzphenanthrene, 89, 97
9,10,-Dibenzyl-1,2,5,6-dibenzanthracene, 90
4,6-Dibromo-Δ^4-cholestenone, 403
9,10-Di-*n*-butyl-9,10-dihydroxy-9,10-dihydro-1,2,5,6-dibenzanthracene, 216
Dicentrine, 39, 40
3,3-Dichloro-7,12-diketocholanic acid, 138
10,10-Dichloro-9-phenanthrone, 11
9,10-Dicyclopentyl-9,10-dihydroxy-9,10-dihydro-1,2,5,6-dibenzanthracene, 386
Diels-Alder reaction, 2-3, 18, 19, 60, 101, 109-110, 173-174, 175, 177, 179, 180, 185, 345, 355-356, 372, 374, 388
Diels hydrocarbon, 159-166, 371
  isolation, 159, 183, 288, 313, 328, 428, 429
  nitroso derivative, 160, 165
  synthesis, 163-165
  tribromo derivative, 165
Diene synthesis, 109-110, 355-356, 388
Diethylaminomethyl-3-phenanthryl carbinol, 46, 47
Digilanidase, 260, 261
Digilanide, A, 259, 260, 261
  B, 259, 260
  C, 259, 260
Digitaligenin, 259, 262
Digitalin, 259, 262
Digitalis, 257
Digitalose, 259, 261, 408, 414
Digitic acid, 335
Digitogenic acid, 325, 328-329, 333, 335, 426
Digitogenin, 323, 324, 325, 326, 328, 329, 425-426
Digitoic acid, 325, 335
Digitonides, 118-120, 249, 285, 322-323, 376, 394, 428
Digitonin, 257, 321-323, 324
  molecular compounds, *see* digitonides
Digitoxandiacid, 289
γ-Digitoxanoldiacid, 279, 280, 289
Digitoxigenin, 259, 276, 290, 413
Digitoxin, 259, 260, 261, 300
  physiological activity, 415
Digitoxose, 259, 261
Digoxigenin, 259, 283, 409-410, 411, 413
Digoxigeninic acid, 283
Digoxigenone, 283
Digoxin, 259, 260, 300, 411-412
Dihydroanthranol, 107, 108
Dihydrocholesterol, analysis, 427
  configuration, 114, 156
  digitonide, 119
  epimerization, 115
  occurrence, 113, 122
  oxidation, 141, 226-227
  preparation, 114, 115, 116
  properties, 113, 392
Dihydrocholesteryl acetate, oxidation, 170, 226-227
Dihydrocodeine, 37
Dihydrocymarin, 301
Dihydrodesoxymorphine-D, 46-47
9,10-Dihydro-1,2,5,6-dibenzanthracene, 90
Dihydrodigoxigenone, 283
Dihydroequilenin, 215, 383
Dihydroequilin, 215
α-Dihydroergosterol, 372, 373
22-Dihydroergosterol, absorption spectrum, 374
  irradiation product, 377, 380
  preparation, 180
α-Dihydrofucosterol, 365
Dihydrogitoxigenin, α-, 277, 278, 279, 280
  β-, 279, 280

Dihydrogitoxigeninic acid, 279
Dihydrolevopimaric acid, 346
Dihydromethylcholanthrene, 355
3,4 - Dihydronaphthalene-1,2-dicarboxylic acid anhydride, 110
3,4-Dihydro-1-naphoic esters, 355
  substituted, 356
Dihydro-oestrone, *see* oestradiol
Dihydro-ouabain, 301
9,10-Dihydrophenanthrene, 9, 12-13, 343
3,4-Dihydrophenanthrene-1,2-dicarboxylic acid anhydride, 221
Dihydro-*d*-pimaric acid, 67, 68
Dihydroprogesterone, 251
Dihydroretene, 344
Dihydrositosterols, 112
22-Dihydrostigmasterol, 357-358
Dihydrostrophanthidin, 264-265
Dihydrostrophanthidinic acid, 264, 265
Dihydrotachysterol, 184
Dihydrothebainone, 37
Dihydrotrianhydrostrophanthidin, 413
Dihydrovitamin D_2, 184, 375
  -maleic anhydride, 185, 186, 377
Dihydroxyabietic acid, 59
3,4-Dihydroxyaporphine, *see* apomorphine
Dihydroxycholadienic acid, α-, 369
  β-, 369
3,12-Dihydroxy-Δ^7-cholenic acid, 132, 282, 368
6,12-Dihydroxychrysene, 21
7,8-Dihydroxy-7,8-di-(α-naphthyl)-acenaphthene, 386
4,4′-Dihydroxydiphenyl, 387
4,4′-Dihydroxydiphenylmethane, 387
3,7-Dihydroxy-12-ketocholanic acid, 138
6,7-Dihydroxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-11,12-dicarboxylic anhydride, 387
3,6-Dihydroxyphenanthrene, 47
3,4-Dihydroxyphenanthrenequinone, *see* morpholquinone
Diketocholanic acid, 3,7-, 139
  3,12-, *see* dehydrodesoxycholic acid
  7,12-, 137
1′,3′-Diketo-1,2-cyclopentenophenanthrene, 343, 388
1′,3′-Diketo-3,4-cyclopentophenanthrene, 343
6,12-Diketohexahydrochrysene, 21, 22
Dimedon derivative, 377
3,5-Dimethoxy-2,6-diethoxyphenanthrene, 40, 41
β-(1,5-Dimethoxy-4-naphthoyl)-propionic acid, 347
5,9 - Dimethoxyphenanthrene - 1,2 - dicarboxylic anhydride, 388
5,9-Dimethoxyphenanthrindanedione, 388
2,3-Dimethyl-6,7-acechrysene, 355
Dimethyl-1,2-benzanthracene, 2′,6-, 89
  2′,7-, 89
  3′,6-, 89
Dimethyl-1,2-benzanthracene, 3′,7-, 89
  5,6-, 88, 89
  5,10-, 350, 353-354
5,6-Dimethyl-1,2-benzanthraquinone, 86
16,20-Dimethylcholanthrene, 107, 349-350, 351
2,3-Dimethylchrysene, 355
9,10 - Dimethyl-9,10-dihydroxy-9,10-dihydro-1,2,5,6-dibenzanthracene, 216
2,2′-Dimethyldiphenyl, 357
8,9-Dimethylene-1,2-benzanthracene, 351
4′,3 - Dimethylene - 1,2,5,6 - dibenzanthracene, 90
1,2-Dimethyl-7-methoxyphenanthrene, 209
Dimethylmorphol, 28-29
  -9-carboxylic acid, 28
1,6-Dimethylnaphthalene, 93
Dimethylphenanthrene, 1,2-, 168-169, 207-208
  1,7-, *see* pimanthrene
  1,9-, 348
1,2-Dimethyl-7-phenanthrol, 207-208
3,8-Dimethylpicene, 423
2,3,8,9-Di-(1′,2′-naphtho)-chrysene, 104-105
Di-(α-naphthyl)-carbinol, 387
α,α′-Dinaphthyl ketone, 103
2,7-Dinitroanthraquinone, 19
Diphenic acid, 1-2, 14
Diphenyl, 1
  -2-acetic acid, 356
  -4-carboxylic acid, 57, 58
  -*o*,*o*′-dialdehyde, 6
  4,4′-dihydroxy-, 387
9,10-Diphenyl-9,10-dihydroxy - 9,10 - dihydro-1,2-benzanthracene, 386
9,10-Di-*i*-propyl-9,10-dihydroxy-9,10-dihydro-1,2,5,6-dibenzanthracene, 386
9,10 - Di - *n* - propyl-9,10-dihydroxy - 9,10-dihydro-1,2,5,6-dibenzanthracene, 216, 385, 386
Disinomenine, 38
Diversine, 38
Dodecahydrocholanthrene, 352
Δ^{11}-Dodecahydrophenanthrone-9, 356
Dodecahydrotriphenylene, 17
Domesticine, 43
Drug addiction, 45-48, 343-344
Duodephanthondiacid, 271, 272, 273

Echinocystic acid, 319, 320
Elbs reaction, 99-108, 354-355
Elemolic acid, 319
Emicymarin, 408
Empirical formulas, from analysis, 426-427
*Epi*allocholesterol, 282, 361, 362
*Epiallo*pregnanol-3-one-20, 404
*Epi*cholesterol, 362-363
*Epi*coprosterol, 116, 228
*Epi*dihydrocholesterol, 114, 115, 116, 119, 228
*Epi*dihydrocinchol, 231

3-*Epi*hydroxyaetio*allo*cholanone-17, 228, *see* androsterone
3-*Epi*hydroxyaetiocholanone-17, 228, 229
3-*Epi*hydroxycoprostanone-24, 369
Epimeric form, 34, 114, 119
*Epi*sitostanol, 231
*Epi*stigmastanol, 231
Epithelioma, 86
Equilenin, 201-202, 211, 212
  dihydro-, 383
  origin, 252, 254
  reduction, 215
Equilin, 201-202
  dehydrogenation, 212-213
  origin, 252, 254
  reduction, 215
Equol, 205
Ergopinacol, 176, 387
Ergostadione-3,6, 172, 173
Ergostane, 172
Ergostatetraene, 381
Ergostatriene, 371
Ergostenediols, 176
Ergostenetriol-I, 174-175
  -II, 172, 174-175
Ergostenols, 371-373
Ergosterol, 112, 113, 118, 171-174
  absorption spectrum, 173, 371, 374
  configuration, 119, 172, 229
  conversion to oestrone, 219, 387
  dehydrogenation, 183
  22-dihydro-, 180, 372, 374, 380
  irradiation, 178-186
  isomers, 373-374
  occurrence, 303, 380
  oestrogenic action, 217
  oxidation, 183
  oxide, 172
  peroxide, 174-175
Ergosterol-B, 374
  -B_2, 374
  -B_3, 374
  -D, 373-374
6-Ethoxy-cholestadiene-4,6-one-3, 403
Ethyl abietate, 62
17-Ethylaetiocholane, *see* pregnane
1-Ethyl-7-isopropylphenanthrene, *see* methylretene
1-Ethyl-7-methylphenanthrene, *see* methylpimanthrene
17-Ethyltestosterone, 395

Fat metabolism, 405
Female hormones, 187, *see also* oestradiol, oestrone, and progesterone
  biological investigation, 190-192, 193
  clinical uses, 215
  isolation, 193-195, 196-199, 214, 383, 385
Fichtelite, 53, 69-70, 427
Fluoranthene, 91, 107
Fluorenone, 15, 55
  -1-carboxylic acid, 107
  dicarboxylic acid, 55, 57
Follicular hormone, 196, *see* oestrone
  α-, 196
  δ-, 195, 382-383
  hydrate, *see* oestriol
Folliculin, 196, *see* oestrone
Fossil resins, 49, 69
Friedel and Crafts reaction, 8-10, 14, 71, 73, 74, 75, 93-94, 98, 99, 100, 102, 105, 340, 343, 347
Friedelin, 424
Friedman test, 190
Fucostanol, 365
Fucosterol, 113, 119, 122

Galactose, 324
Galipot, 50, 52
Gamabufogenin, 305, 311-312, 421
Gamabufotalin, *see* gamabufogenin
Gamabufotoxin, 305, 311
Genetic relationships, alkaloids, 43-45
  bile acids, 127-129
  heart poisons, 316
  sex hormones, 251-255, 404
  sterols, 120-123
Genins, *see* cardiac aglycones, bufagins
Girard's reagent, 197-198, 201, 230, 383-384, 404, 406
Gitogenic acid, 326-327, 328-329, 425
  oxidation, 332-333
Gitogenin, 323, 324, 325, 326, 328, 329, 425, 427
Gitonin, 258, 321-322, 324
Gitoxigenin, 259, 262, 263, 276-282, 290
Gitoxigenone, 278
Gitoxin, 259, 260, 300
Glaucine, 39-40
Glucose, 258, 259, 260, 319, 324
Glucuronic acid, 194, 319
Glycocholic acid, 124
Glycodesoxycholic acid, 125, 368
Glycyrrhetic acid, 319
Gonadotropic hormones, 188, 189-190
Gypsogenin, 319, 423

Hatcher method, 299
Haworth's synthesis, *see* succinic anhydride synthesis
Heart poisons, 256
  plant, 256-302, 408-419
  toad, 256, 302-316, 419-422
Hederagenin, 319, 320, 423
Hederin, 319
Hemolysis, 322
Heptaacetylanhydroouabain, 292
Heptaacetyldesoxydihydroouabain, 293
Heptacosane, 205
Heterografts, 87
5,6,11,12,13,14-Hexahydrochrysenes, 21-22
Hexahydrodianhydrogitoxigenin, 279
Hexahydromethylcholanthrene, 352
5,8,9,10,13,14-Hexahydrophenanthrene-13-carboxylic acid, 355
1,2,3,6,7,8-Hexahydropyrene, 17, 99

Hexahydroscillaren A, 298
Hexose, 259
Hippulin, 201-202, 252, 254
Homoretene, *see* methylretene
Hydrindenes, 79, 159, 370
Hydrobufotalin, 307
Hydrocarbon, $C_{21}H_{16}$, from anhydrouzarigenin, 288
  $C_{21}H_{16}$, from cholic acid, 158, 370
  C_{27},H_{44}, from *epi*allocholesterol, 282, 362
Hydrofluorenes, 79
Hydrogenation, analytical, 182-183, 374
  biological, 122, 123, 127-128, 249, 253, 255
  halogen compounds, 30, 209
  hydrogen donors, 185-186, 213
  phenanthrene, 12-13, 343
  resin acids, 59, 67
  resistance to, 132, 176, 265, 274, 294, 368, 372, 385, 411, 414, 416
  ring cleavage, 266, 272, 279-280, 295-296, 307-308, 314
  with selenium, 159, 185-186
  stereochemical course, 115-117, 134
Hydrophenanthrenes, 12-13, 71
3-Hydroxy-7-acetoxy-12-ketocholanic acid, 138, 139
3-Hydroxyaetio*allo*cholanic acid, 231
3-Hydroxyaetio*allo*cholanone-17, 227, 228, *see* isoandrosterone
Δ^5-3-Hydroxyaetio*allo*cholenone-17, *see* dehydroisoandrosterone
3-Hydroxy-Δ^5-aetiobilianic acid, 394
3-Hydroxyaetiocholanone-17, 288
Hydroxy*allo*cholanic acid, 3-, 156-157, 170, 231, 370
  6-, 366
$4'$-Hydroxybenzpyrene, 98-99
3-Hydroxybisnor*allo*cholanic acid, 248, 249
3-Hydroxybisnorcholenic acid, 170, 247, 248, 394
7-Hydroxycholanic acid, 138, 139, 366
Hydroxycholanic acids, 137-139, 365-366
3-Hydroxy-Δ^5-cholenic acid, 370, 393
7-Hydroxycholestene, 371
Hydroxycholesterol, $7(\alpha)$-, 180, 381
  $7(\beta)$-, 381
3-Hydroxy-7,12-diketocholanic acid, 138
Hydroxyfluorene carboxylic acid, 15
3-Hydroxy-6-keto*allo*cholanic acid, 127
3-Hydroxy-6-ketocholanic acid, 156
3-Hydroxy-12-ketocholanic acid, 127
Hydroxy ketone, m. p. 194° (*see allo*pregnanol-3-one-20), 242, 243, 245, 248-249, 402
Hydroxy-1-keto-1,2,3,4-tetrahydrophenanthrene, 7-, 221-222
  8-, 388
  9-, 388
7-Hydroxy-7-methylcholesterol, 380
4-Hydroxy-5,6-methylenedioxyaporphine, *see* pukateine.
3-Hydroxynor*allo*cholanic acid, 231
1-Hydroxyphenanthrenequinone, 6
1-Hydroxy-1,2,3,4-tetrahydrophenanthrene, 386
Hydoesoxycholic acid, 125-126, 155, 156
Hypophysectomy, 189

Indanes, 78
Indene-1,2-dicarboxylic acid, 220
Indenes, 79, 220
1-Iodoacenaphthene, 108
Ionones, 78
Isoagathic acid, 68-69
Iso*allo*lithobilianic acid, 156
Iso*allo*pregnanedione, 249
Iso*allo*pregnanol-3-one-20, 249
Isoandrosterone, 227, 228, 229
Isobilianic acid, 143
Isobufocholanic acid, 127, 308
"Isocholesterol," 358
Isocodeine, 34
Isocorydine, 42, 43
Isodesoxybilianic acid, 140, 141, 143
Isodigitoxigenic acid, 276, 279, 280
Isodigitoxigenin, 276
Isodigoxigenin, 283
Isogitoxigenic acid, 279, 280
Isogitoxigenin, 277
Isogitoxigeninic acid, 277
Isolithobilianic acid, 143, 156
"Isolithobilianic" acid, 151
Isomerization, anhydrogamabufogenin, 305
  bile acids, 132, 155
  cardiac aglycones, 266, 267, 270, 277, 278-279, 279-280, 283, 284, 291, 410, 416
  digitogenic acid, 325
  hormones, 249, 404
  α-methylmorphimethine, 26
  resin acids, 49-50, 51, 52, 68, 345
  sterols, 116, 119, 134, 174, 175, 179, 181, 371-374
Isonoragathic acid, 69
Isoouabain, 291, 294
α-Isoperiplogenic acid, 275, 276
Isoprene rule, 59, 66, 67, 68, 320
Isopropyl-1,2-benzanthracene, 3-, 89
  6-, 89, 94
  7-, 89, 94
  10-, 89, 351
1-Isopropylnaphthalene, 93
7-Isopropyl-1-naphthyl methyl ether, 347
Isopyrovitamin, 181, 182
Isosarmentogenin, 410
Isoscillaridinic acid, 297
α-Isostrophanthic acid, 267
α-Isostrophanthidic acid, 267, 275, 276
α-Isostrophanthidindiacid, 268
α-Isostrophanthidinic acid, 268
Isostrophanthin, 266-267
Isothevetin, 414
Isouzarin, 284

Kauri copal, 49, 68
3-Ketobisnor*allo*cholanic acid, 250
3-Ketobisnorcholanic acid, 250
3-Keto-4-bromocholanic acid, 403
3-Ketocholanic acid, 403
12-Ketocholanic acid, 138
  degradation, 153
  pyrolysis, 167, 168
3-Keto-Δ^4-cholenic acid, 255, 370, 403
7-Ketocholesteryl chloride, 363
Ketodecahydrochrysenes, 389
3′-Keto-3,4-dihydro-1,2-cyclopentenophenanthrene, 388
7-Keto*epi*cholesterol, 363
1-Keto-1,2,3,4,9,10-hexahydrophenanthrene, 388
Ketohydroxyoestrin, 196, *see* oestrone
Ketone reagents, 197-198, 201, 230, 383-384, 404, 406
1-Keto-1,2,3,4,5,6,7,8-octahydroanthracene, 216-217, 386
6-Ketotestosterone, 397
4′-Keto-1′,2′,3′,4′-tetrahydrobenzpyrene, 98
Keto-1,2,3,4-tetrahydrophenanthrene, 1-, 11, 72, 216, 222
  4-, 72, 216

Lactone ring of heart poisons, 265-268, 296, 301, 309-310, 408-409
Lagodesoxycholic acid, α-, 367
  β-, 367
Lanosterol, 113, 358, 424
Laudanine, 43
Laudanosine, 43, 44-45
Laureline, 42
Laurepukine, 42-43
Laurotetanine, 41-42, 43
Lecithin, 123
Legal test, 265-266
Levopimaric acid, 50, 51, 68, 186, 344-347
Liebermann *or* Liebermann-Burchard reaction, 59, 117, 233, 306, 311, 360
Lifschütz reaction, 117
Lithobilianic acid, 143, 150, 155-156
Lithocholic acid, 123, 124, 126
  configuration, 229
  degradation, 154-155
  dehydration, 124, 366
  isolation, 125, 367
  preparation, 138, 139
  preparation from cholesterol, 370
Loewe and Moore test, 224
Lumistanol, 376
Lumisterol, 179, 181, 182, 183, 184, 186, 375-376
Luteosterone, 244, *see* progesterone
  C, 243
  D, 243

Male hormones, 188, 224-240, 394, *see also* androsterone, testosterone
  bio-assay, 236-237, 394, 396-397
Male hormones, biological investigation, 192-193
Manganese resinate, 52
Manila copal, 68
Marinobufagin, *see* bufagin
Marrian crystals, 201, *see* oestriol
Menformon, 196, *see* oestrone
Metastasis, 85
β-*m*-Methoxybenzoylpropionic acid, 222, 389
Methoxycyclopentenophenanthrene, 7-, 210, 219
  8-, 389
  9-, 389
9-Methoxy-1,2,5,6-dibenzanthracene, 90
7-Methoxy-3,4-dihydro-1-naphthoic acid, 356
7-Methoxy-3,3′-dimethyl-1,2-cyclopentenophenanthrene, 211, 212
3-Methoxyhexahydrophenanthrene-13-carboxylic acid, 356
7-Methoxy-1-keto-1,2,3,4,9,10-hexahydrophenanthrene, 223, 390
7-Methoxy-1-keto-2-methyl-1,2,3,4,9,10-hexahydrophenanthrene, 390
7-Methoxy-1-ketooctahydrophenanthrene, 390
7-Methoxy-3′-methyl-1,2-cyclopentenophenanthrene, 211-212
3-Methoxy-5,6-methylenedioxyaporphine, *see* laureline
β-(2-Methoxy-1-methyl-6-napthoyl)-propionic acid, 347
Methoxy-1-methylphenanthrene, 2-, 347
  7-, 347
γ-3-Methoxy-4-methylphenylbutyric acid, 388
γ-(6-Methoxy-1-naphthyl)-butyric acid, 388
γ-(6-Methoxy-1-naphthyl)-ethyl alcohol, 388
9-Methoxyphenanthrene, 341
Methoxyphenanthrene-1,2-dicarboxylic anhydride, 7-, 388
  9-, 388
γ-*m*-Methoxyphenylbutyric acid, 222, 389
9-Methoxyretene, 347
6-Methoxy-1-tetralone, 388
β-(6-Methoxy-1-tetralyl)-ethyl alcohol, 388
d-7-Methoxythebainone, *see* sinomenine
7-Methoxy-1-vinylnaphthalene, 387
17-Methylandrostanediol-3,17, 235
17-Methylandrostane-3-ol-17, 240
Methyl-1,2-benzanthracene,2′-, 89
  3-, 89
  3′-, 89
  4-, 89
  5-, 88, 350, 354
  6-, 88
  7-, 89
  10-, 350, 351, 354
o-Methylbenzophenones, 100

2-Methyl-3,4-benzphenanthrene, 357
3′(or 2′)-Methyl-1,2-benzpyrene, 90
7-Methyl-4-bromohydrindone-1, 106, 107
Methylcholanthrene, from bile acids, 85-86, 167-168
  carcinogenic action, 87, 88, 92, 349
  -choleic acid, 131, 352
  dihydro-, 355
  oxidation, 86
  synthesis, 105-106, 354-355
Methyl-1,2-cyclopentenophenanthrene, 1′-, 160
  2′-, 160
  3′-, *see* Diels hydrocarbon
Methyl-1,2,5,6-dibenzanthracene, 2′-, 90
  3′-, 90
Methyldihydrophenanthrenes, 72
7-Methyl-8,9-dimethylene-1,2-benzanthracene, 351
7-Methylenecholesterol, 381
1′,9-Methylene-1,2,5,6-dibenzanthracene, 90, 106, 350
Methylenedioxydihydroxyaporphine, *see* lauropukine
Methylisohexyl ketone, 136, 328
1-Methyl-7-isopropylphenanthrene, *see* retene
N-Methyllaurotetanine, 43
Methylmorphenol, 27
Methylmorphimethine, α-, 26-27, 282, 293
  β-, 26-27, 36-37
Methylmorphol, 26, 29
Methylnaphthalene, α-, 73, 93
  β-, 74, 94
5-Methyl-2′,1′-naphtho-1,2-fluorene, 370
1-Methyl-3-naphthoic acid, 79
Methylnaphthylamine sulfonic acid, 73
Methylphenanthrene, 1-, 72
  2-, 73
  3-, 73
  4-, 72, 80
  9-, 30-31, 38
1-Methyl-3-phenanthroic acid, 80
Methylpimanthrene, 66, 75
Methylreductinic acid, 419
2-Methylpyrene, 162
Methylretene, 62, 64, 65, 75
17-Methyltestosterone, 240, 394-395, 404
4-Methyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid, 65, 80
4-Methyl-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid, 65, 79
Microhydrogenation, 183, 374
Mimusopssapogenin, 319
Monobasic acid, $C_{27}H_{42}O_5$ (from tigogenin), 330, 333
Morphenol, 27-28
Morphine, 24-37, 343-344
Morphol, 27, 28, 29
  cleavage, 25-28
  -quinone, 27
Naphthacene, 19, 20, 91
1,2-Naphthalene dicarboxylic acid anhydride, 94, 353
1,2-Naphthalic anhydride, *see* 1,2-naphthalene dicarboxylic acid anhydride
β-Naphthoylhydrindenes, 106
β-(1-Naphthoyl)-propionic acid, 71
β-(2-Naphthoyl)-propionic acid, 71
β-Naphthylacetic acid, 97-98
β-Naphthylamine, 353
γ-(1-Naphthyl)-butyric acid, 71, 72
γ-(2-Naphthyl)-butyric acid, 71, 72
1-β-Naphthylhydrindene, 109
β-Naphthyl methyl ether, 209, 347
β-Naphthylmethyl ketone, 98
α-Naphthyl paraconic acid, 11
Narcotine, 43
Natelson-Gottfried synthesis, 391
Neoergosterol, 176-177, 217, 387
Neopine, 37
Nitration, phenanthrene, 8
Nitrobenzene, solvent, 9, 74, 340, 347
Nitropapaverine, 40
Nitrophenanthrene, 2-, 8
  3-, 8
  4-, 8
  9-, 8
Nor-acid, definition, 66
Nor*allo*cholanic acid, 171, 172, 289
Noraporphine, 41
Norcholanic acid, 146
Nor-*m*-hemipinic acid, 40
Norlithocholic acid, 231
Normal series, 114
Norsolannelic acid, *see* biloidanic acid
Norsterol, 374
Nutriacholic acid, 126

1,2,3,4,5,6,7,8-(*s*)-Octahydrophenanthrene, 12, 13
1,2,3,4,9,10,11,12-(*as*)-Octahydrophenanthrene, 13, 76, 77, 78, 99, 348
as-Octahydrophenanthrone-9, 356
Octahydrotrianhydroperiplogenin, 284-285
Octanthrene, *see* *s*-octahydrophenanthrene
Oestradiol, 188
  dehydration of methyl ether, 211-212
  isolation, 214, 385
  monobenzoate, 214, 383
  origin, metabolism, 252, 253-254
  preparation, 213, 385
Oestranediol-3,17, 385
Oestriasterol, 365
Oestrin, 188, 189, 196, 199-200, 352, 384
Oestriol, 200-201
  alkali fusion, 207
  degradation products, 215, 385
  glucuronide, 382
  occurrence, 199, 200, 381
  origin, 252, 254
  triacetate, 201

Oestrogenic hormones, 193-194
  bio-assay, 191-192
  and cancer, 217-218, 352
  colorimetric determination, 382
  origin, 252-254, 405
  synthetic approach, 219-224, 387-391
  use in therapy, 215
Oestrogenic substances, synthetic, 215-217, 385-387
  bio-assay, 387
  use in therapy, 215
Oestrone, 188
  benzoate, 214, 218
  bio-assay, 191-192
  and cancer, 218
  estimation, 194-195
  esters, 382
  hydrogenation, 226, 384-385, 391-392
  isolation, 193, 194, 197-198, 199, 383
  origin and metabolism, 252, 253-254
  preparation from ergosterol, 219, 387
  properties, 195
  sources, 192, 193, 196-199
  structure, 205-212, 387
  X-ray analysis, 206, 384
Oestrus, 188
Oleandrin, 259, 262
Oleanolic acid, 319, 320, 321, 423
Oleoresin, acids, 49-50, 51
  primary constituents, 68, 344-347
Onocerin, 358-359, 424
Opium alkaloids, 44
Ouabagenin, 259, 261
Ouabaic acid, 291
Ouabain, 259, 261, 290-295, 300, 413-414
Oxidation (*see* dehydrogenation)
  anhydrodihydrostrophanthidin, 285-286, 412
  aromatic hydrocarbons, 3, 14-15, 17, 18, 54, 86, 107
  aromatization, 60, 172, 183, 274, 294-295, 390
  biological, 44, 251-253, 255, 316
  influence of configuration, 141, 336
  perbenzoic acid titration, 59, 183, 346, 375, 412, 414
  phenolic compounds, 6, 38
  photochemical, 174, 175, 176
  -reduction potentials, 340
  selenium dioxide, 365-366
  sterol side chain, 136-137, 146, 154, 170-171, 227-228, 230, 231, 234, 246
  tertiarily bound hydrogen, 56, 335
Oxindole, 31
Oxodigitogenic acid, 325-326, 335, 426
Oxydigitogenic acid, *see* oxodigitogenic acid

Palmitic acid, 394, 396
Panaxsapogenin, 319
Papaverine, 40, 43
Papilloma, 86
Parigenin, 324, *see* sarsasapogenin
Parillin, 324
Pentacosane, 205
Perbenzoic acid titration, 59, 183, 346, 375, 414
Perhydrodehydrolumisterol, 376
Perhydropyrocalciferol, 376
Periplocin, 259
Periplogenin, 259, 263, 275-276, 290, 413
Perlman-Davidson-Bogert synthesis, 22, 77-80, 108, 161, 164, 167, 210, 348, 370
Perrier method, 9
Perylene, 16, 18
  -3,10-quinone, 18
Phenanthraldehyde, 1-, 340, 342
  2-, 10-11
  3-, 10-11
  9-, 10-11, 340
Phenanthraphenazine, 15
Phenanthrene, 1-15
  bond structure, 2-3
  bromine addition, 6-7, 339-340
  derivatives, 10-13, 344
  oxidation, 14-15
  substitutions, 7-10, 340
  synthesis, 76-77, 110, 355-357
Phenanthrene alkaloids, 24-28
Phenanthrene dibromide, 6-7, 339-340
Phenanthrene-1,2-dicarboxylic anhydride, 221
  derivatives, 388
Phenanthrene-disulfonic acids, 8
  -1-sulfonic acid, 8
  -2-sulfonic acid, 8
  -3-sulfonic acid, 8
  -9-sulfonic acid, 8
Phenanthrenequinone, 11, 14-15
  syntheses, 5-6
1,2-Phenanthrenequinone-4-sulfonate, 13
3,4-Phenanthrenequinone-1-sulfonate, 13
Phenanthroic acid, 1-, 10, 342
  2-, 10
  3-, 10
  9-, 10
Phenanthrol, 1-. 11
  2-, 3, 11, 14
  3-, 3, 11, 14, 47
  4-, 11-12
  9-, 11, 341-342, 356, 357
Phenanthrylamine, 1-, 342
  2-, 342
  3-, 342
  9-, 342
4,5-Phenanthrylenemethane, 16, 17
Phenanthryl halides, 342-343
2-Phenylcyclohexanol, 356
2-Phenylcyclohexanone, 356
4-(β-Phenylethyl)-hydrindone-1, 391
Phenyltrimethylammonium hydroxide, 25
β-Phocaecholic acid, 126
Phthalic anhydride synthesis, 93-96
Physostigmine, 304
Phytosterols, 112, 120, 121, 169-186
Phytosynthesis of alkaloids, 40, 43-45

Picene, 16, 18, 158, 159
  homologues from sapogenins, 319, 423, 424
  synthesis, 22
Picrates, 5, 102
Pimanthrene, 66, 67, 69
  -quinone, 75
  synthesis, 75
Pimaric acid, *d*-, 52-53, 66-67, 344, 345
  l-, 50, 51, 68, 186, 344-346
Pinabietic acid, 51
Pinic acid, 50
Porphyroxine, 38
Precision combustion, 427
Pregnancy, diagnosis, 190
Pregnane, 203, 204
Pregnanediol, 202-205
  origin, 253, 254
  relation to progesterone, 245, 247-248
Pregnanedione, 203
  activity, 250-251
  bromination, 249
  conversion to progesterone, 247-248
Pregnanol-20-one-3, 248
Δ^4-Pregnenedione-3,20, *see* progesterone
Δ^5-Pregnenedione-3,20, 404
Δ^5-Pregnenol-3-one-20, 246, 247, 394
  rôle in metabolism, 251, 252, 253
Pro-abietic acid, 345, 347
Procaine, 45
Progesterone, 188
  activity of derivatives, 250-251, 403-404
  bio-assay, 193, 241-242
  function, 240-242
  isolation, 244-245, 402
  origin and metabolism, 251-253
  polymorphism, 243, 402
  properties, 245
  structure, 245-250
Progesterone, *α*-, 244
  β-, 244, 383
Progestin, 188-189, 244
Progynon, 196
Progynon B oleosum, 214
Prolan, 190
Prosolannelic acid, 142, 143, 147
Provitamin D, 178, 378, 380
Pschorr synthesis, 28-31, 32, 33, 39, 40, 41, 70, 96-98, 343
Pseudobufotalin, 313-314
Pseudocholestane, *see* coprostane
Pseudocholestene, 134
Pseudocodeine, 35
Pseudostrophanthidin, 270
Pukateine, 42
Pyrene, 16, 17-18, 91, 98, 343
  purification, 20
  -quinone, 17
Pyridazine derivatives, 157, 158, 171, 173
Pyroabietic acids, 51
Pyrocalciferol, 181, 182, 184, 376
Pyrocholoidanic acid, 142, 145
Pyrodesoxybilianic acid, 145-146, 153
Pyroquinovic acid, 368, 424
Pyrosolannelic acid, 142

Quericicobufagin, 316
Quillaiasapogenin, 319
Quinovic acid, 368, 424
Quinovin, 424

Rat unit of oestrone, 191-192
Rearrangements (*see also* isomerization)
  alkyl *o*-naphthoylbenzoic acids, 104
  allylic, 35, 175, 280, 366
  Beckmann, 11, 342
  benzilic acid, 15, 55, 144
  o-benzoylbenzoic acids, 96
  dehydrogenation, 20, 158-159, 162, 166, 167
  Elbs reaction, 103, 104
  morphine-apomorphine, 31
  o-naphthoylnaphthoic acids, 95-96
  oxidation, 172
  ring closure, 156
  β,γ-unsaturated ketones, 359
  Wagner-Meerwein, 65, 211-212, 274-275, 287, 293, 294, 315
  Walden inversion, 230, 233, 392, 393
Reduction methods, *see* hydrogenation
  aluminum isopropylate, 240, 282, 361
  anthrones, 93, 109
  aroyl acids, 72, 93, 98
  Bouveault, 62
  conjugated systems 173
  Grignard, 354, 395
  halides, 11, 40, 134, 336-337
  modified Clemmensen, 72, 137, 347, 389
  ring cleavage, 27, 37
  stannous chloride, 341
  α,β-unsaturated ketones, 361
  Wolff-Kishner, 65, 138, 363, 423
Regularobufagin, 316
Resene, 50
Resin acids, 49-70
  primary, 68, 344-347
Retene, 53-58, 344, 346
  oxidation, 64
  syntheses, 74-75, 77
Retenequinone, 54, 55-56, 343, 347
9-Retenol, 347
Rhamnose, 259, 261, 290, 419
Rickets, 177-178
Robinson-Rapson synthesis, 222-223, 389
Robinson-Schlittler synthesis, 223, 389-390
Rosenheim color reaction, 117, 118, 298, 359-360
Rosenmund reaction, 10
Rosenmund-von Braun reaction, 354
Rosin, 49, 52
  isomerization, 50-52

Salkowski reaction, 117
l-Sapietic acid, 68

- Sapinic acids, 50, 68
- Sapocholic acid, 367-368
- Sapogenins (sterol-like), 323-337, 424-428
  - correlations, 328-329
  - degradation, 330-331
  - dehydrogenation, 327-328
  - side chain, 331-334
- Sapogenins (triterpenoid), 318-321, 422-424
- Saponins, 317-318
  - digitalis, 321-323
  - triterpenoid, 318-319
- Sapotalene, 318, 319, 422
- Sarcoma, 84, 87
- Sarmentocymarin, 259, 410, 411, 412
- Sarmentogenin, 259, 410-411, 413
- Sarmentose, 259, 261
- Sarsasapogenic acid, 336, 337
- Sarsasapogenin, 324, 327, 329, 336-337, 427-428
  - dehydrogenation, 327-328
- Sarsasapogenone, 428
- Sarsasapogenyl chloride, 336, 337
- α-Scillanic acid, 296
- Scillaren A, 259, 260, 295, 298, 299
  - activity, 300, 301
- Scillaridin A, 259, 262, 295-299
- Scillaridinic acid, 297
- Scymnol, 128-129, 335
- Selenium, dehydrogenation, 58, 149, 158, 358, 391, 424, 428, 429
  - hydrogenation, 159, 185-186
- Selenium dioxide, 365, 369, 373
- Senso, 302
- Sex hormones, 187-255
  - biogenetic relationships, 251-255
  - biological investigation, 190-193
  - female, 193-217, 240-251
  - gonadotropic, 188, 189-190
  - male, 224-240
  - relation to cancer, 217-219, 352
  - standardization, 196, 383
  - synthetic approach, 219-224, 387-391
- Siaresinolic acid, 319
- Sinomenine, 37, 343
- Sitosterol, 112, 119, 121, 229, 357-358
  - α_1- and α_2-, 358
  - β-, 357-358
  - γ-, 113
- Smilagenin, 324, 425
- Sodium resinate, 52
- Solanidiene, 427
- Solanidine, 428-429
- Solanine, 428
- Solannelic acid, 142, 147
- Solanocapsidine, 429
- Solanocapsine, 429
- Solanthrene, 428
- Sonn and Müller reaction, 11, 340, 341
- Spiran formation, 162, 348, 370
- Squalene, 255
- Squill, 257
- Staden's acid, 156
- Stephen synthesis, 341
- Stereochemical influence, androgenic activity, 229, 395
  - bromination, 249-250, 402
  - cardiac activity, 285, 300-301, 411-412, 415-416
  - cyclization, 343
  - hydrogenation, 115-117, 134, 395
  - oxidation, 141, 336
- Stereochemical nomenclature, 398-401
- Stereochemistry, cardiac aglycones, 290, 411, 413, 414-415
  - sapogenins, 428
  - sterols, bile acids, 113-117, 154, 155-157, 227, 229, 231, 359, 375-376, 387
- Steric hindrance, 13-14, 61, 63, 69, 74, 137, 138, 265, 267-268, 283, 287, 343, 353, 390, 401, 410, 411, 417
- Sterocholic acid, 128
- Steroids, 359
- Sterols, 111-123, 133-187
  - *allo*-series, 114
  - bacteria, 365
  - color reactions, 117-118
  - dehydrogenation, 158-159, 166, 371
  - description, 111-113
  - function, 122
  - glycosides, 382
  - lower animals, 121-122, 364-365
  - metabolism, 122-123, 251, 255
  - origin, 120-122, 255
  - phytosterols, 169-174
  - position of methyl groups, 152-154, 371, 387
  - purification, 113, 118, 119, 120, 178
  - side chain, 167-169, 227
  - stereochemistry, 113-117, 154, 155-157, 227, 229, 231, 359, 375-376, 387
  - β-type, 114, 119
- Stigmastanedione-3,6, 171
- Stigmastanol, 365
- Stigmasterol, 112, 169-171
  - configuration, 119, 229
  - conversion to hormones, 234, 246-247
  - properties, 113, 119
- Strophanthidin, 258, 259, 260, 263-273, 417
  - activity, 300
  - configuration, 290, 413
  - dehydrogenation, 287-288
  - early formula, 286-287
- Strophanthidinic acid, 264, 267-268, 269, 270, 408
- Strophanthidonic acid, 264, 269
- Strophanthin, 257
  - k-, 258, 260, 300
  - g-, *see* oubain
- k-Strophanthin-β, 258, 259
- Strophanthobiase, 260
- Strophanthus species, 257, 258
- Styryl 430, *see* 2-(*p*-aminostyryl)-6-(*p*-acetylaminobenzoylamino)-quinoline methoacetate

Suberylarginine, 304, 305
Substance 248, *see* toxisterol
Substitution reactions, *α*-methylnaphthalene, 73
  β-methylnaphthalene, 74
  phenanthrene, 7-10, 340
Succinic anhydride synthesis, 71-75, 98-99, 208
Sumaresinolic acid, 319, 320, 423
Suprasterol I, 181, 182, 183, 186
  II, 181, 182
Surface film measurements, 208, 423, 427
Syntheses, general methods, aldehyde, 10-11, 340-341
  Bardhan, 220, 387-388
  Bardhan-Sengupta, 76-77, 108, 109, 160-161, 220
  Chuang, 391
  Darzens, 79-80, 348
  diene, 109-110, 355-356, 388
  Elbs, 99-108, 354-355
  Natelson-Gottfried, 391
  Perlman-Davidson-Bogert, 22, 77-79, 108, 161, 164, 167, 210, 348, 370
  phthalic anhydride, 93-96
  Pschorr, 28-31, 32, 33, 39, 40, 41, 70, 96-98, 343
  Robinson-Rapson, 222-223, 389
  Robinson-Schlittler, 223, 389-390
  succinic anhydride 71-75, 98-99, 208

Tachysterol, 179, 181, 182, 183-184, 186
Taurocholic acid, 124
Taurodesoxycholic acid, 125
Terpene hydrocarbons, 49
α-Terpineol, 323
Tertiary group, definition, 58-59
Testalolone, 394
Testicular hormone, function, 224
  isolation, 238, 240
  see testosterone
Testosterone, 188, 236-240
  activation by X-substance, 396-397
  derivatives, 394-396
  isomers, 395
  origin and metabolism, 252, 253-254, 255
Testriol, 394
4,4,5,6-Tetrabromocholestanone-3, 403
Tetrahydroabietic acid, 59, 62, 63
Tetrahydroanhydrodesoxyuzarigenin, 284, 288
Tetrahydroanhydrodigitoxigenin, 279
Tetrahydroanhydrodigitoxigenone, 415
Tetrahydroanhydrodigoxigenone, 409
Tetrahydroanhydro-uzarigenins, 284, 285
1′,2′,3′,4′-Tetrahydro-1,2-benzpyrene, 90, 98
Tetrahydrobufagin, 314
Tetrahydrolevopimaric ester, 346
3-(1,2,3,4-Tetrahydroisoquinolino)-4-hydroxy-1,2,3,4-tetrahydrophenanthrene, 47
ac-Tetrahydro-*β*-naphthol, 323
d-Tetrahydropalmitin, 44
Tetrahydrophenanthrene-1,2-dicarboxylic anhydride, 387
β-Tetralone, 414
Tetrahydroxyabietic acid, 59
Tetrahydroxyaporphine, 2,3,5,6-, 39
  3,4,5,6-, 42
1,2,5,6-Tetramethylnaphthalene, 359
Tetraphenylmethane, 92, 352
Thebaine, 24, 25, 29, 37
Thebainone, 37
Thebaol, 29
Theelin, 195, *see* oestrone
Theelol, 201, *see* oestriol
Thelephoric acid, 22-24
Thevetigenin, 414-415
Thevetin, 300, 414-416
Thilobilianic acid, 150, 151
Tiglic acid, 319
Tigogenin, 324, 327, 328-329, 330, 335-336, 427
Tigogenone, 336
Tigonin, 322, 324, 424
Toad Poisons, 302-316, 419-422
  basic constituents, 303-304, 419
  cardiotonic constituents, 304-306
o-Toluyl-*α*-naphthoic acid, 353
Toxisterol, 181
Triacetyl digitogenin, 325
Trianhydrostrophanthidin, 274-275, 286, 287
Tribasic acid, $C_{21}H_{30}O_7$, from gitogenic acid, 332, 333
  $C_{27}H_{40}O_8$, from gitogenic acid, 332-333
  B($C_{27}H_{38}O_9$) from digitogenic acid, 333, 334, 425
4,5,6-Tribromocholestanone, 403
Trihydroxybufosterocholenic acid, $C_{28}H_{46}O_5$, 128, 366-367
2,5,4′-Trihydroxydiphenyl, 23-24
Trihydroxyisosterocholenic acid, 367
3,4,5-Trihydroxyphenanthrene, 27, 28
Trihydroxysterocholanic acid lactone, 368
Triketocholanic acid, 3,7,12-, *see* dehydrocholic acid
  4(?),7,12-, 129
Trimethoxyphenanthrene-9-carboxylic acid, 3,4,5-, 29
  3,4,7-, 29
  3,4,8-, 32, 35
Trimethylaminoacetohydrazide hydrochloride, *see* Girard's reagent
Trimethylnaphthalene, 1,2,5-, 69, 423
  1,2,7-, *see* sapotalene
1,2,5-Trimethyl-6-naphthol, 423
1,2,7-Trimethylnaphthol, 319, *see*, 1,2,5-trimethyl-6-napthol
1,2,8-Trimethylphenanthrene, 358
3,9,10-Trimethylpicene, 422
Trinitrobenzene complexes, 102-103
Triphenylbenzene, 92, 352, 427
Triphenylene, 16-17, 18, 91
Triterpene alcohols, 319, 358-359

Triterpenoid sapogenins, 318-321, 422-424
Tschopp test, 229, 235
Tschugajeff reaction, 117
β-Type configuration, 114, 119, 120

Undephanthontriacid dimethyl ester, 271-272
Ursocholanic acid, 127
Ursodesoxycholic acid, 126, 366
Ursolic acid, 318, 423
Uzarigenin, 283-290, 413
Uzarin, 259, 261, 284, 285, 300-301, 415
Uzaron, 257

Vallicepobufagin, 316
Veridobufagin, 316
1-Vinylnaphthalene, 388
17-Vinyltestosterone, 395
Vitamin D, 177-178, 179-180, 181, 186, 377-381
  absorption spectrum, 178, 179, 380
  colorimeitric determination, 379
  isolation, 378-380
Vitamin D_1, 179
Vitamin D_2, 179-180, 181, 182, 183, 184
  maleic anhydride addition, 185-186
  oestrogenic action, 217
  structure, 184-186, 376-377
Vitamin D_3, 379, 380, 381

Wagner-Meerwein rearrangement, 65, 211-212, 274-275, 293, 294, 315
Walden inversion, 230, 233, 392-393
Wolff-Kishner reduction, 65, 138

X-ray studies, 149-150, 164, 173, 206, 308, 312, 314, 370, 384, 389, 390, 421, 427
X-substance, 396
Xylindein, 24
Xylose, 324

Zerewitinoff test, adrenal cortex substances, 407, 408
  cardiac aglycones, 265, 266, 408, 416, 417, 418
  toad poisons, 421
Zymosterol, 112, 113